A. Mohamed
446109

TSCA INFORMATION NOW CURRENT THROUGH July 7, 2001

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

Customers running searches and/or SDIs in the H/Z/CA/CAplus files incorporating CAS Registry Numbers with the P indicator between 12/27/01 and 1/23/02, are encouraged to re-run these strategies. Contact the CAS Help Desk at 1-800-848-6533 in North America or 1-614-447-3698, worldwide, or send an e-mail to help@cas.org for further assistance or to receive a credit for any duplicate searches.

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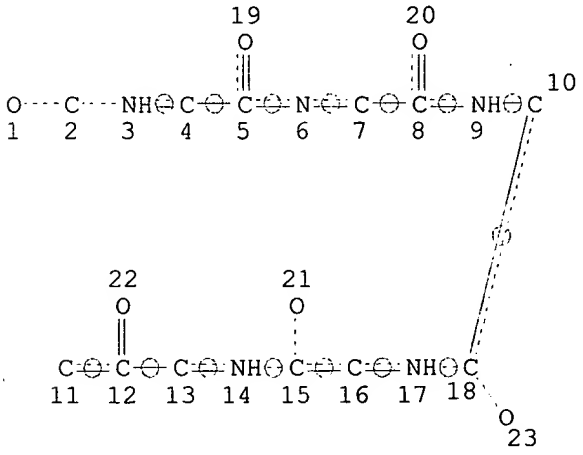

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GRAPH ATTRIBUTES:
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Searched by: Mary Hale 308-4258 CM-1 12D16

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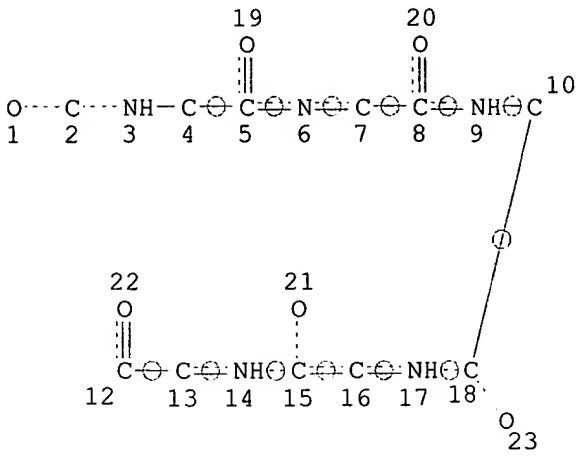

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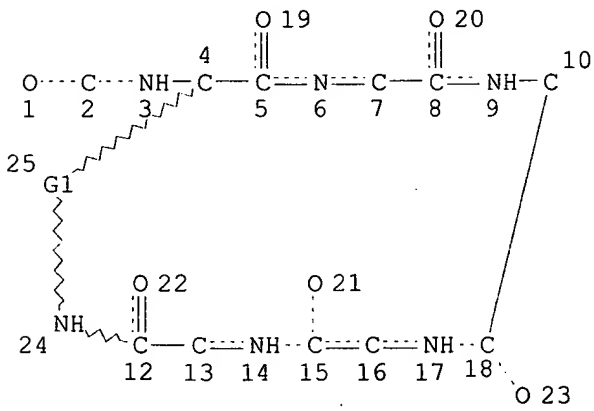

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NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
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100.0% PROCESSED 9337 ITERATIONS 314 ANSWERS
SEARCH TIME: 00.00.02

Searched by: Mary Hale 308-4258 CM-1 12D16

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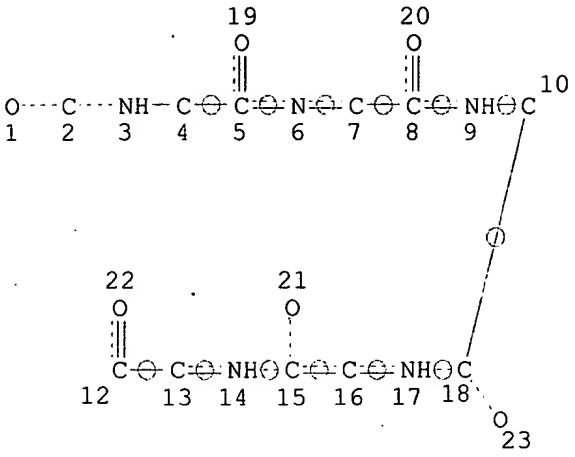

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NUMBER OF NODES IS 22

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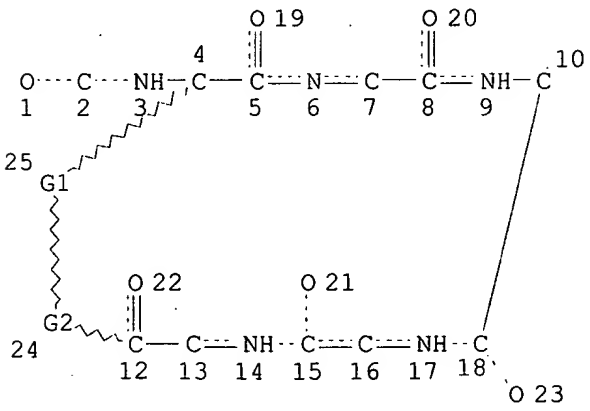

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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 24

STEREO ATTRIBUTES: NONE
L12 25 SEA FILE=REGISTRY SUB=L8 SSS FUL L11

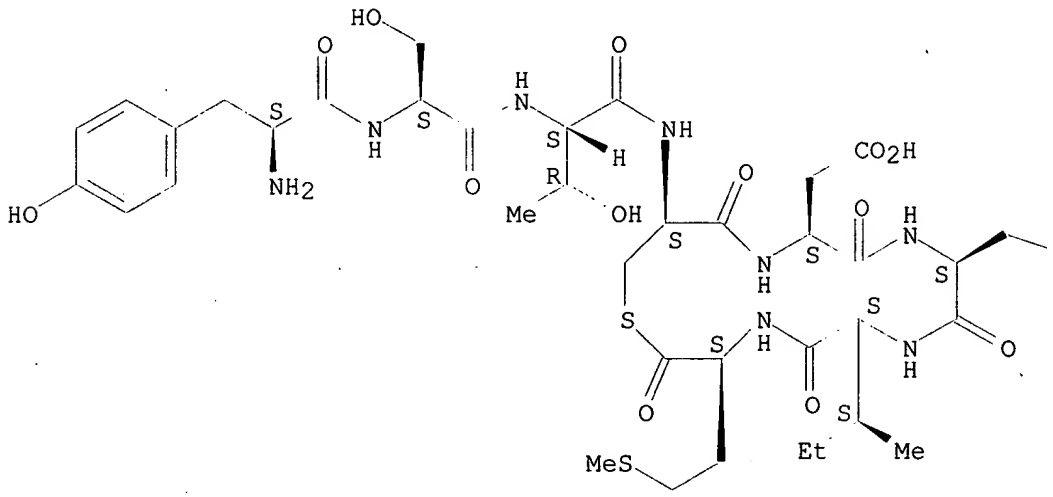
Searched by: Mary Hale 308-4258 CM-1 12D16

100.0% PROCESSED 1276 ITERATIONS 25 ANSWERS
SEARCH TIME: 00.00.02

L12 ANSWER 1 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-33-0 REGISTRY
CN L-Methionine, L-tyrosyl-L-seryl-L-threonyl-D-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

Searched by: Mary Hale 308-4258 CM-1 12D16

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

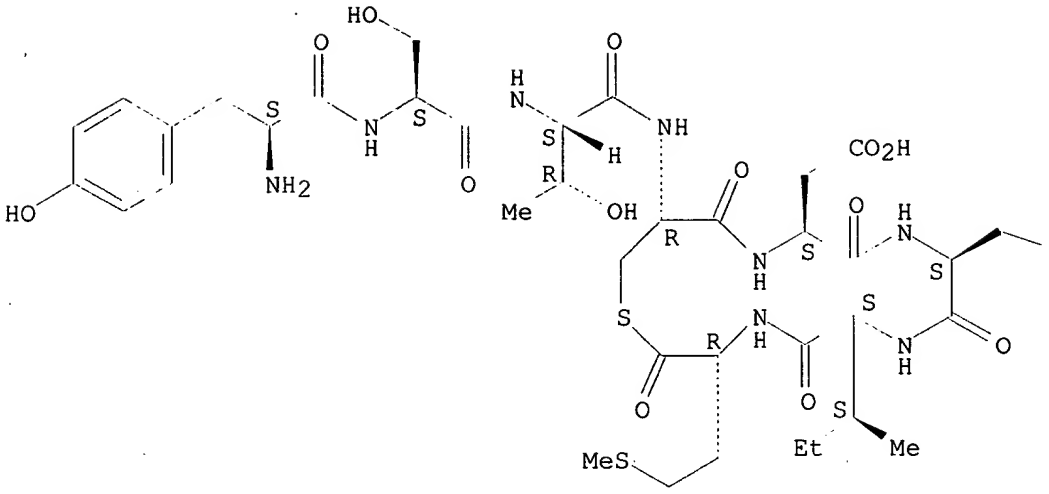
AB In S. aureus, the agr locus is responsible for controlling virulence gene expression via quorum sensing. As the blockade of quorum sensing offers a novel strategy for attenuating infection, novel insights into the structure, activity and turnover of the secreted staphylococcal auto-inducing peptide (AIP) signal mols. were sought. A series of analogs (including the L-alanine and D-amino acid scanned peptides) was synthesized to det. the functionally crit. residues within the S. aureus group I AIP. As a consequence, it was established that (i) the group I AIP is inactivated in culture supernatants by the formation of the corresponding methionyl sulfoxide; and (ii) the group I AIP lactam analog retains the capacity to activate agr, suggesting that covalent modification of the AgrC receptor is not a necessary prerequisite for agr activation. Although each of the D-amino acid scanned AIP analogs retained activity, replacement of the endocyclic amino acid residue (aspartate) located C-terminally to the central cysteine with alanine converted the group I AIP from an activator to a potent inhibitor. The screening of clin. S. aureus isolates for novel AIP groups revealed a variant that differed from the group I AIP by a single amino acid residue (aspartate to tyrosine) in the same position defined as crit. by alanine scanning. Although this AIP inhibits group I S. aureus strains, the producer strains possess a functional agr locus dependent on the endogenous peptide and, as such, constitute a 4th S. aureus AIP pheromone group (group IV). The addn. of exogenous synthetic AIPs to S. aureus inhibited the prodn. of toxic shock syndrome toxin (TSST-1) and enterotoxin C3, confirming the potential of quorum-sensing blockade as a therapeutic strategy.

L12 ANSWER 2 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-32-9 REGISTRY
CN D-Methionine, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A



PAGE 1-B

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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Searched by: Mary Hale 308-4258 CM-1 12D16

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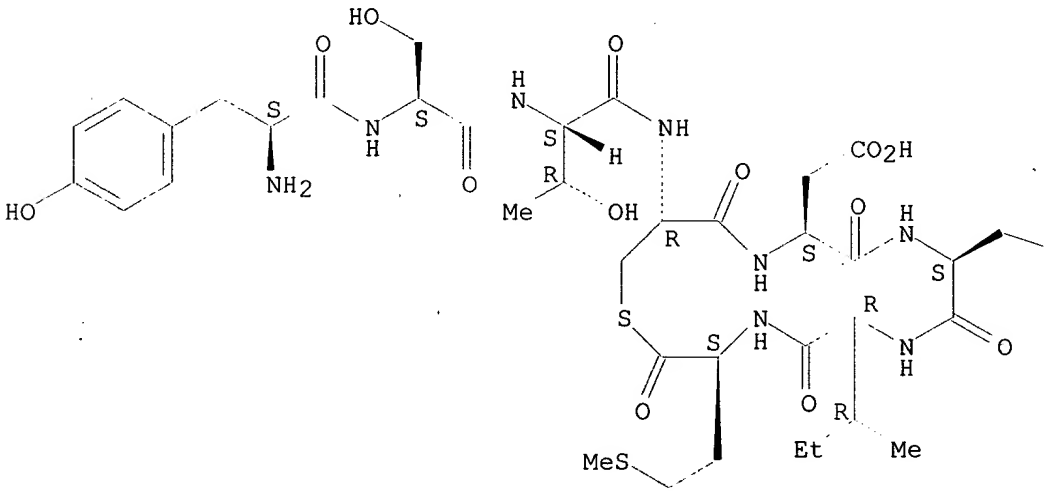
L12 ANSWER 3 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-31-8 REGISTRY
CN L-Methionine, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-D-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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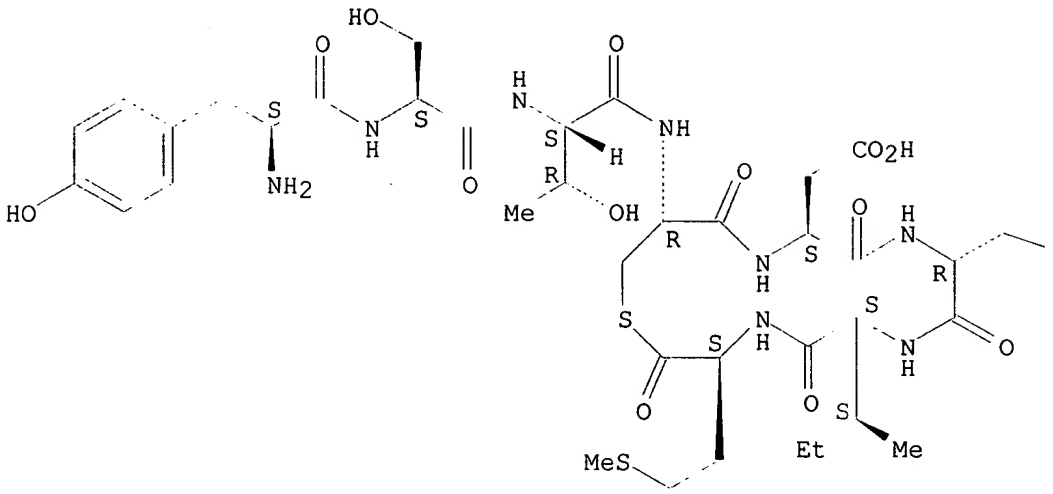
L12 ANSWER 4 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-30-7 REGISTRY
CN L-Methionine, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-D-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2

Searched by: Mary Hale 308-4258 CM-1 12D16

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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Searched by: Mary Hale 308-4258 CM-1 12D16

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L12 ANSWER 5 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-29-4 REGISTRY
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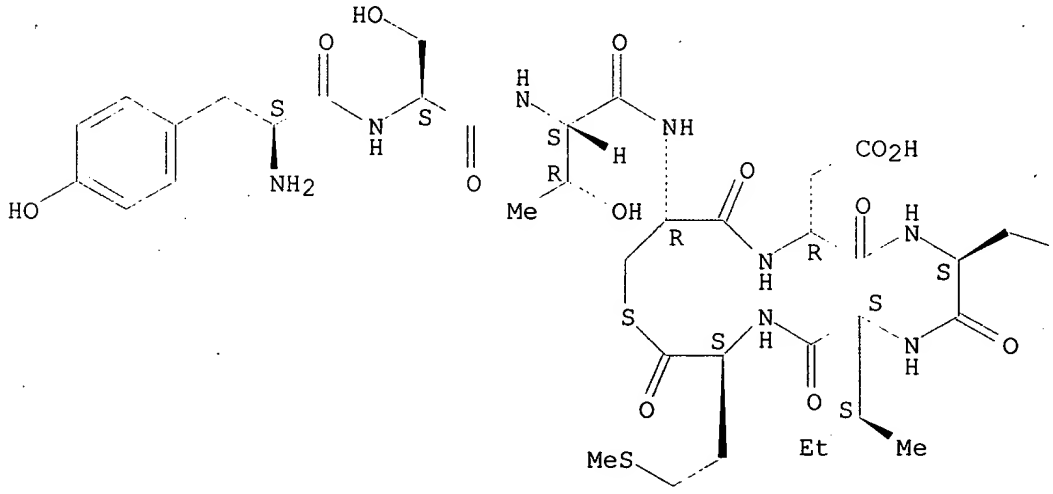
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16

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PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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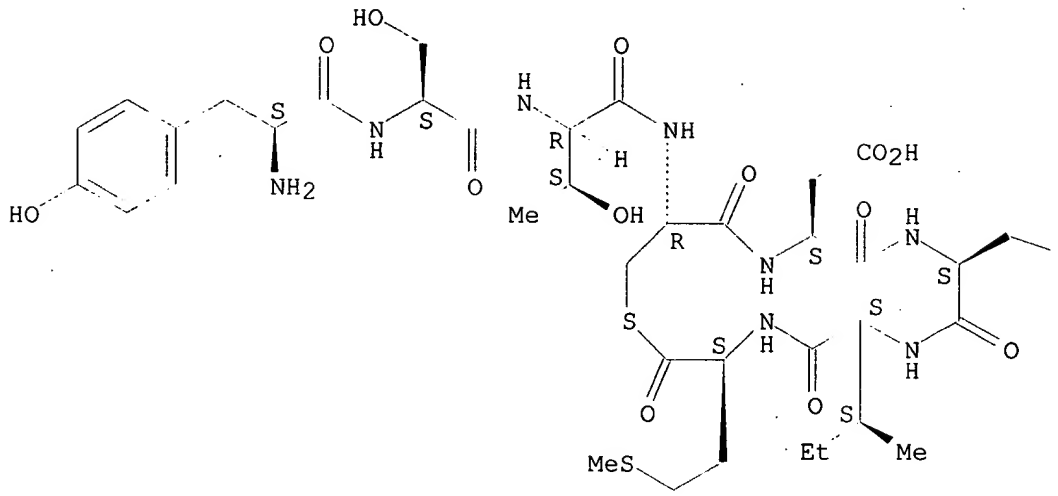
L12 ANSWER 6 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-28-3 REGISTRY
CN L-Methionine, L-tyrosyl-L-seryl-D-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2

Searched by: Mary Hale 308-4258 CM-1 12D16

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

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1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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L12 ANSWER 7 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-26-1 REGISTRY
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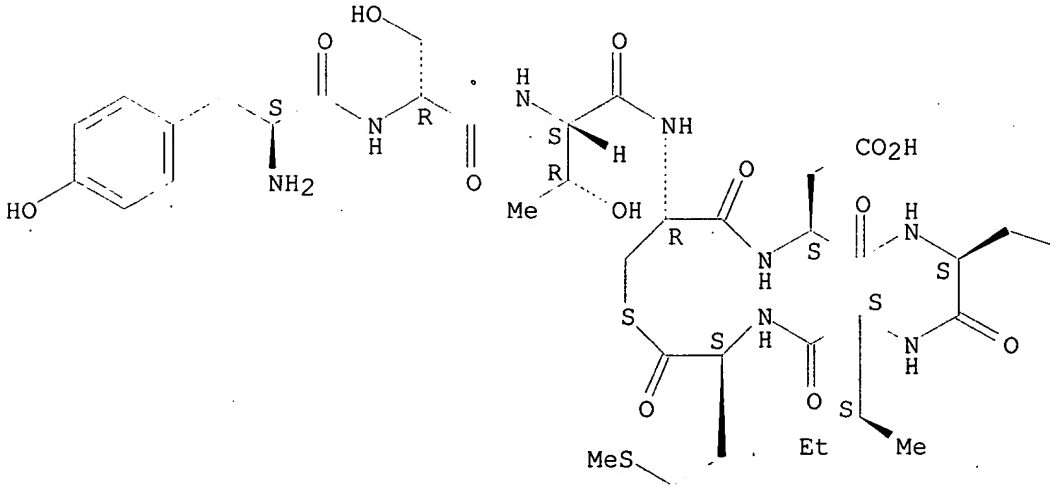
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16

Ph

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1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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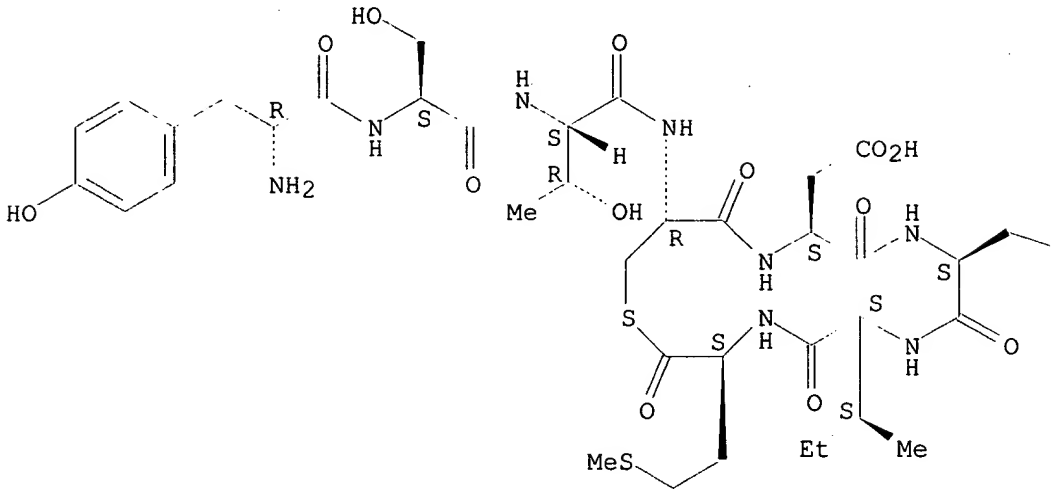
L12 ANSWER 8 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-25-0 REGISTRY
CN L-Methionine, D-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O13 S2

Searched by: Mary Hale 308-4258 CM-1 12D16

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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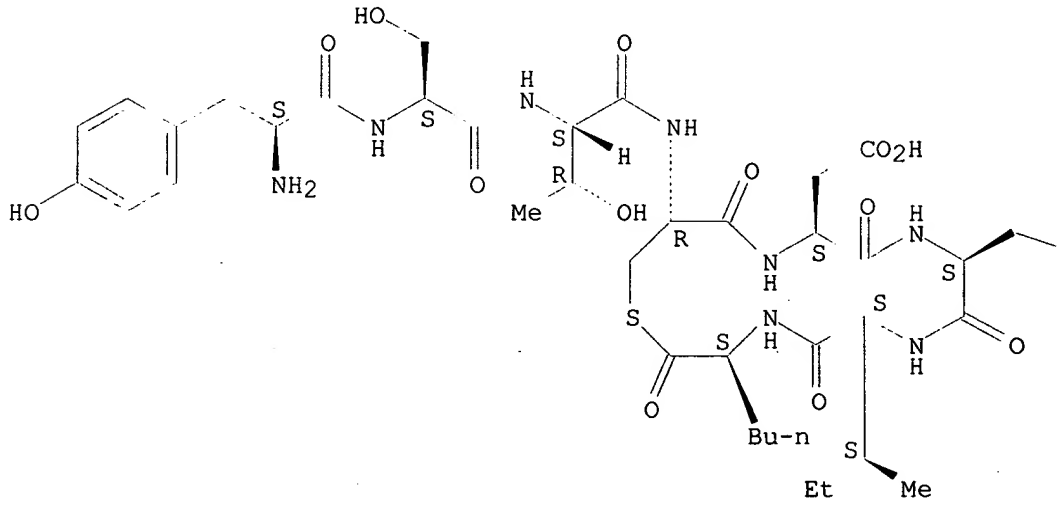
L12 ANSWER 9 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-24-9 REGISTRY
CN L-Norleucine, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C44 H62 N8 O13 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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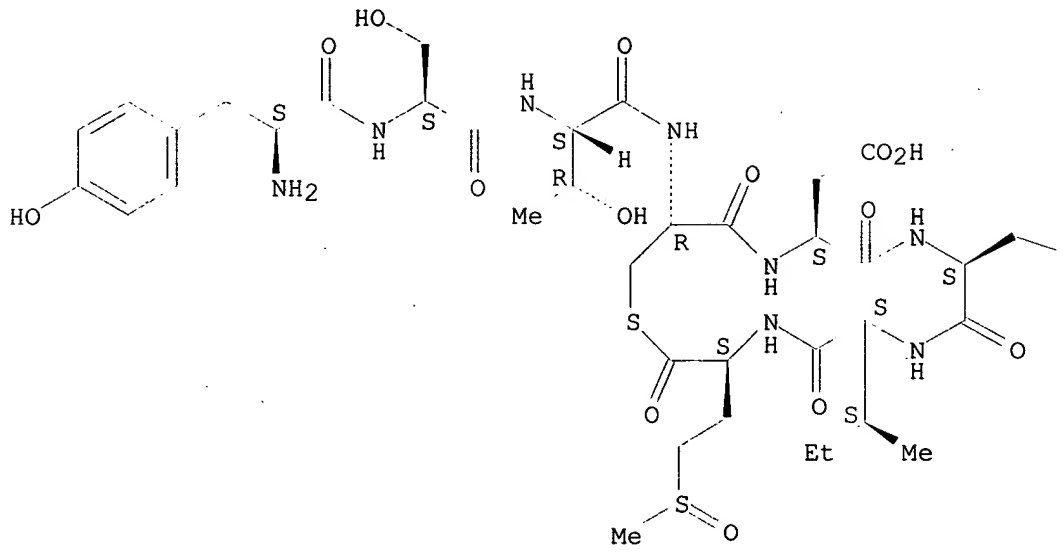
L12 ANSWER 10 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-23-8 REGISTRY
CN Butanoic acid, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-2-amino-4-(methylsulfinyl)-, (8.fwdarw.4)-thiolactone, (2S)- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C43 H60 N8 O14 S2

Searched by: Mary Hale 308-4258 CM-1 12D16

SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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Searched by: Mary Hale 308-4258 CM-1 12D16

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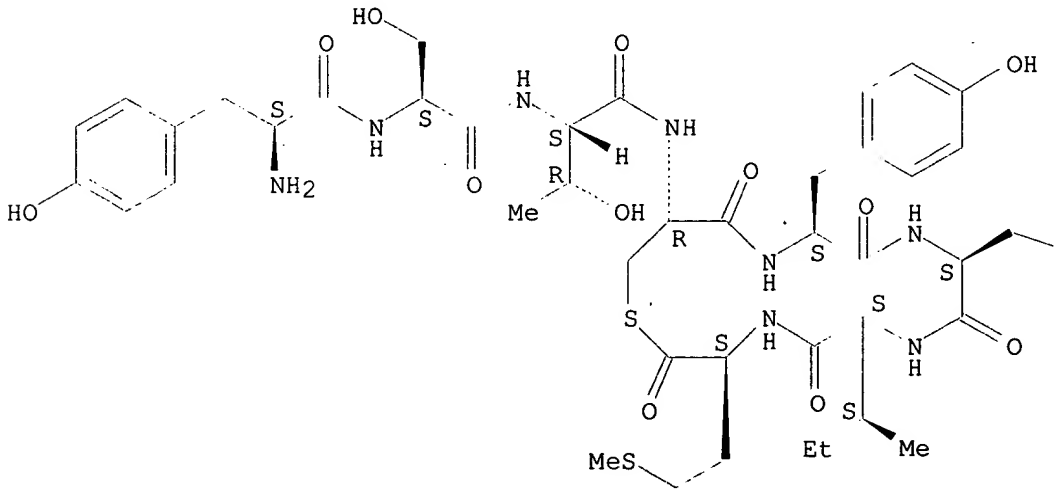
L12 ANSWER 11 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 366803-22-7 REGISTRY
CN L-Methionine, L-tyrosyl-L-seryl-L-threonyl-L-cysteinyl-L-tyrosyl-L-phenylalanyl-L-isoleucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C48 H64 N8 O12 S2
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16

Ph

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

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L12 ANSWER 12 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 321862-05-9 REGISTRY
CN L-Phenylalanine, N-acetyl-L-cysteinyl-L-seryl-L-seryl-L-leucyl-, (5.fwdarw.1)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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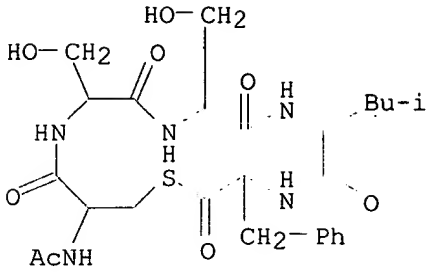
SR CA

Searched by: Mary Hale 308-4258 CM-1 12D16

LC STN Files: CA, CAPLUS, TOXCENTER



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

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REFERENCE 2: 134:128415 Rational design of a global inhibitor of the virulence response in Staphylococcus aureus, based in part on localization of the site of inhibition to the receptor-histidine kinase, AgrC. Lyon, Gholson J.; Mayville, Patricia; Muir, Tom W.; Novick, Richard P. (Laboratory of Synthetic Protein Chemistry, The Rockefeller University, New York, NY, 10021, USA). Proceedings of the National Academy of Sciences of the United States of America, 97(24), 13330-13335 (English) 2000. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

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AB Two-component signaling systems involving receptor-histidine kinases are ubiquitous in bacteria and have been found in yeast and plants. These systems provide the major means by which bacteria communicate with each other and the outside world. Remarkably, very little is known concerning the extracellular ligands that presumably bind to receptor-histidine kinases to initiate signaling. The two-component agr signaling circuit in Staphylococcus aureus is one system where the ligands are known in chem. detail, thus opening the door for detailed structure-activity relationship studies. These ligands are short (8- to 9-aa) peptides contg. a thiolactone structure, in which the .alpha.-carboxyl group of the C-terminal amino acid is linked to the sulfhydryl group of a cysteine, which is always the fifth amino acid from the C terminus of the peptide. One unique aspect of the agr system is that peptides that activate virulence expression in one group of S. aureus strains also inhibit virulence expression in other groups of S. aureus strains. Herein, it is demonstrated by switching the receptor-histidine kinase, AgrC, between strains of different agr specificity types, that intragroup activation and intergroup inhibition are both mediated by the same group-specific receptors. These results have facilitated the development of a global inhibitor of virulence in S. aureus, which consists of a truncated version of one of the naturally occurring thiolactone peptides.

L12 ANSWER 13 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 234451-29-7 REGISTRY
CN L-Phenylalanine, L-seryl-L-valyl-L-cysteinyl-L-alanyl-L-seryl-L-tyrosyl-, (7.fwdarw.3)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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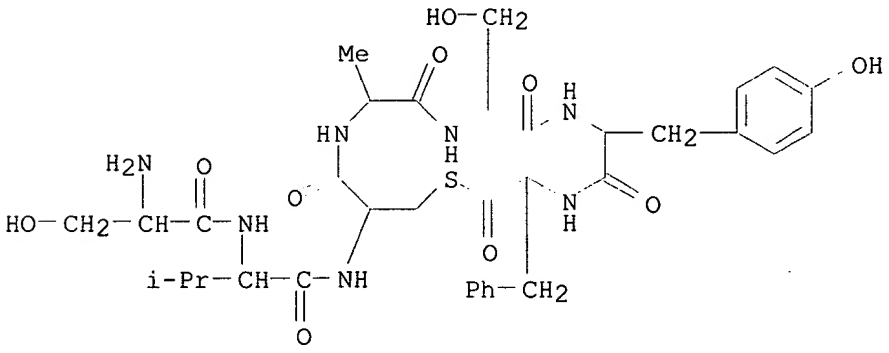
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:127502 Inhibition of virulence factor expression in Staphylococcus aureus by the Staphylococcus epidermidis agr pheromone and derivatives. Otto, Michael; Sussmuth, Roderich; Vuong, Cuong; Jung, Gunther; Gotz, Friedrich (Mikrobielle Genetik, Universitat Tubingen, Tubingen, 72076, Germany). FEBS Lett., 450(3), 257-262 (English) 1999. CODEN: FEBLAL. ISSN: 0014-5793. Publisher: Elsevier Science B.V..

AB The agr quorum-sensing system in Staphylococci controls the prodn. of surface proteins and exoproteins. In the pathogenic species Staphylococcus aureus, these proteins include many virulence factors. The extracellular signal of the quorum-sensing system is a thiolactone-contg. peptide pheromone, whose sequence varies among the different staphylococcal strains. We demonstrate that a synthetic Staphylococcus epidermidis pheromone is a competent inhibitor of the Staphylococcus

Searched by: Mary Hale 308-4258 CM-1 12D16

aureus agr system. Derivs. of the pheromone, in which the N-terminus or the cyclic bond structure was changed, were synthesized and their biol. activity was detd. The presence of a correct N-terminus and a thiolactone were abs. prerequisites for an agr-activating effect in S. epidermidis, whereas inhibition of the S. aureus agr system was less dependent on the original structure. Our results show that effective quorum-sensing blockers that suppress the expression of virulence factors in S. aureus can be designed based on the S. epidermidis pheromone.

L12 ANSWER 14 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 234451-28-6 REGISTRY
CN L-Phenylalanine, glycyl-L-.alpha.-aspartyl-L-seryl-L-valyl-L-cysteinyl-L-alanyl-L-seryl-L-tyrosyl-, (9.fwdarw.5)-thiolactone (9CI) (CA INDEX NAME)
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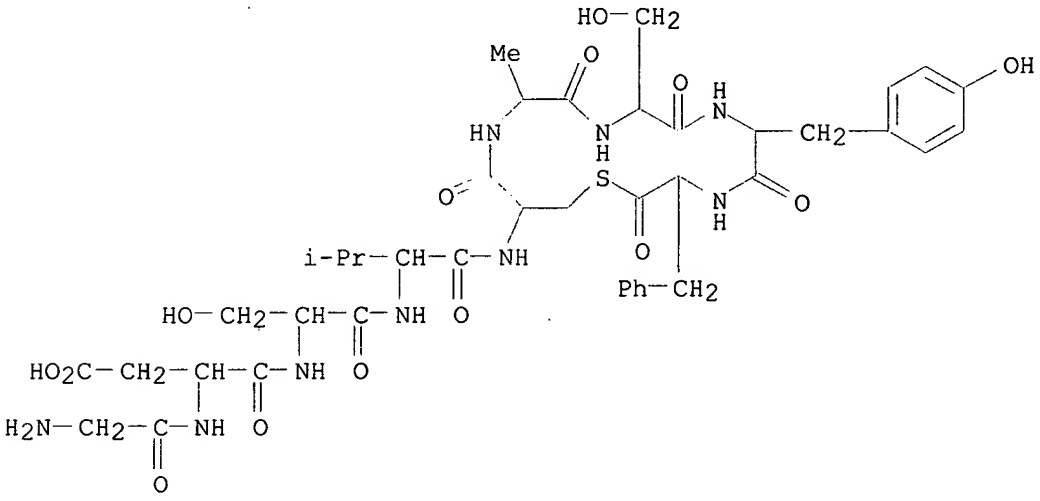
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER



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can be designed based on the S. epidermidis pheromone.

L12 ANSWER 15 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 234451-26-4 REGISTRY
CN L-Phenylalanine, L-.alpha.-aspartyl-L-seryl-L-valyl-L-seryl-L-alanyl-L-seryl-L-tyrosyl-, (8.fwdarw.4)-lactone (9CI) (CA INDEX NAME)
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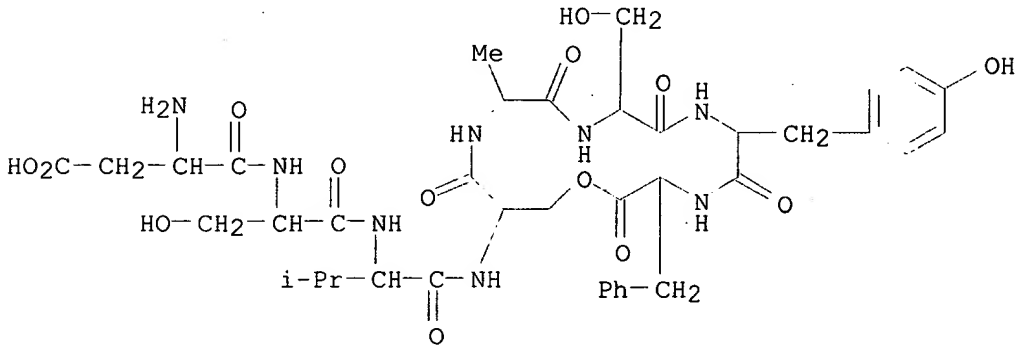

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L12 ANSWER 16 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 234451-25-3 REGISTRY
CN L-Phenylalanine, L-.alpha.-aspartyl-L-seryl-L-valyl-L-cysteinyl-L-alanyl-L-seryl-L-tyrosyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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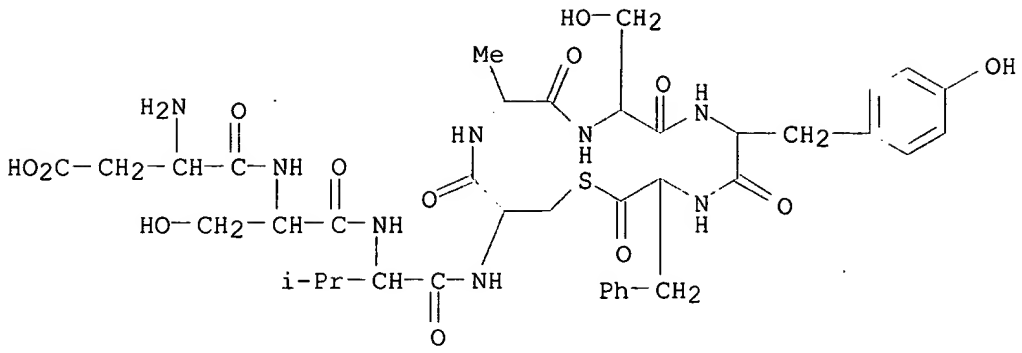
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Searched by: Mary Hale 308-4258 CM-1 12D16



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1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

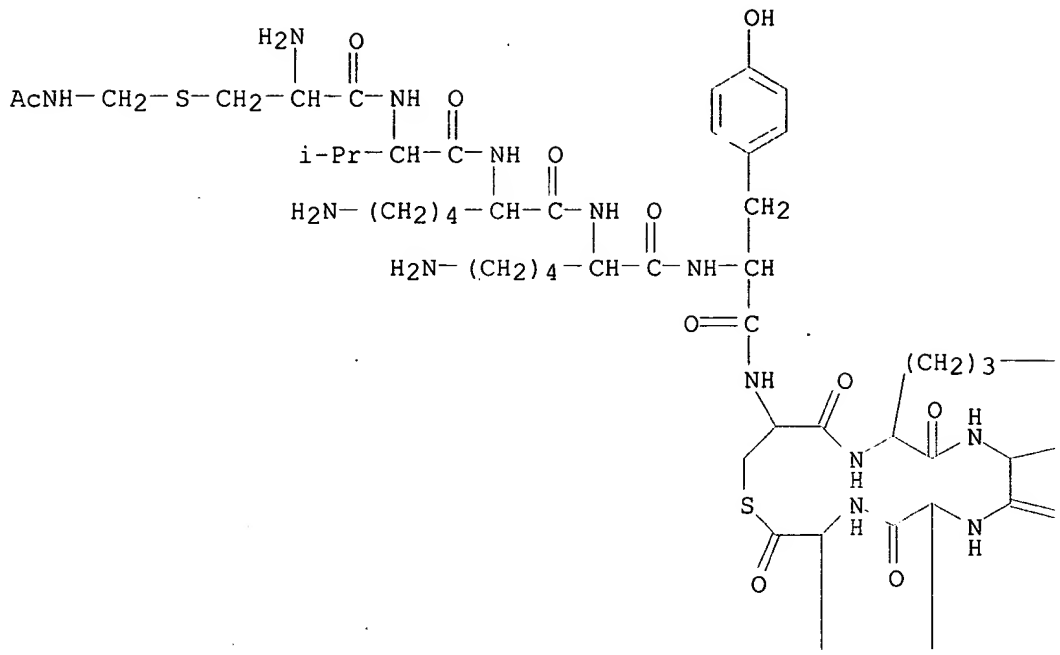
REFERENCE 1: 131:127502 Inhibition of virulence factor expression in Staphylococcus aureus by the Staphylococcus epidermidis agr pheromone and derivatives. Otto, Michael; Sussmuth, Roderich; Vuong, Cuong; Jung, Gunther; Gotz, Friedrich (Mikrobielle Genetik, Universitat Tubingen, Tubingen, 72076, Germany). FEBS Lett., 450(3), 257-262 (English) 1999. CODEN: FEBLAL. ISSN: 0014-5793. Publisher: Elsevier Science B.V..

AB The agr quorum-sensing system in Staphylococci controls the prodn. of surface proteins and exoproteins. In the pathogenic species Staphylococcus aureus, these proteins include many virulence factors. The extracellular signal of the quorum-sensing system is a thiolactone-contg. peptide pheromone, whose sequence varies among the different staphylococcal strains. We demonstrate that a synthetic Staphylococcus epidermidis pheromone is a competent inhibitor of the Staphylococcus aureus agr system. Derivs. of the pheromone, in which the N-terminus or the cyclic bond structure was changed, were synthesized and their biol. activity was detd. The presence of a correct N-terminus and a thiolactone were abs. prerequisites for an agr-activating effect in S. epidermidis, whereas inhibition of the S. aureus agr system was less dependent on the original structure. Our results show that effective quorum-sensing blockers that suppress the expression of virulence factors in S. aureus can be designed based on the S. epidermidis pheromone.

L12 ANSWER 17 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 226721-13-7 REGISTRY
CN L-Phenylalanine, S-[(acetylamino)methyl]-L-cysteinyl-L-valyl-L-lysyl-L-lysyl-L-tyrosyl-L-cysteinyl-L-arginyl-L-arginyl-L-arginyl-, (10.fwdarw.6)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C62 H102 N22 O12 S2
SR CA
LC STN Files: CA, CAPLUS

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A



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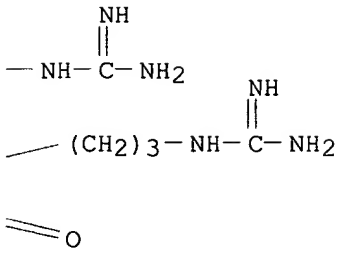

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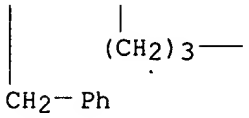

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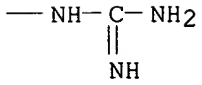

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:32149 Thia Zip Reaction for Synthesis of Large Cyclic Peptides: Mechanisms and Applications. Tam, James P.; Lu, Yi-An; Yu, Qitao (Department of Microbiology and Immunology, Vanderbilt University, Nashville, TN, 37232-2363, USA). J. Am. Chem. Soc., 121(18), 4316-4324 (English) 1999. CODEN: JACSAT. ISSN: 0002-7863. Publisher: American Chemical Society.

AB This paper describes the mechanism and application of an efficient thia zip cyclization that involves a series of intramol. rearrangements in a cysteine-rich peptide for the synthesis of large end-to-end cyclic peptides. Key functional groups required in this reaction include an N.alpha.-cysteine, a thioester, and at least one internal free thiol in a peptide. The zip reaction is initiated by intramol. trans-thioesterification through an internal thiol with the thioester. A thio-lactone is formed under ring-chain tautomeric equil. that favors ring formation in aq. buffered soln. at pH > 7. Successive ring expansions through thiol-thio-lactone exchanges in the direction of the amino terminus lead finally to a large N.alpha.-amino thio-lactone which then undergoes a spontaneous and irreversible ring contraction through a sequence-independent S to N acyl isomerization to form an end-to-end lactam. The reversible thio-lactone exchanges are sequence-dependent, and the rate-detg. steps are shown by rate studies on model peptides. The assistance of internal thiols in reducing the ring sizes and hence the entropy of the thio-lactone exchanges correlates well with cyclization rates. Zip-assisted end-to-end cyclizations forming 93- and 99-atom rings through a series of small thio-lactone intermediates were 60-200-fold faster under strongly denaturing conditions such as 8 M urea than the corresponding unassisted lactamization. The thia zip reaction has been applied successfully to the synthesis of a 31-amino acid cyclic peptide, the naturally occurring cyclopsychotride that shows the antimicrobial activity. In addn., the thia zip reaction also enables the synthesis of an engineered cyclic 33-amino acid animal defensin by replacing the end-to-end disulfide with a lactam, which retains the antimicrobial activities of the native open-chain form.

L12 ANSWER 18 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 225784-73-6 REGISTRY
CN L-Methionine, N-acetyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-isoleucyl-, (5.fwdarw.1)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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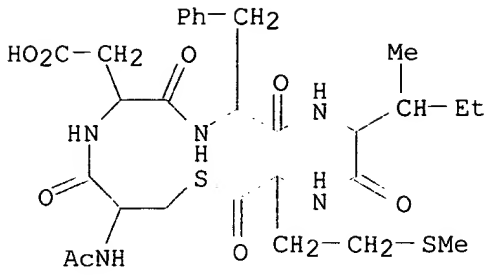
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Searched by: Mary Hale 308-4258 CM-1 12D16



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

AB In S. aureus, the agr locus is responsible for controlling virulence gene expression via quorum sensing. As the blockade of quorum sensing offers a novel strategy for attenuating infection, novel insights into the structure, activity and turnover of the secreted staphylococcal auto-inducing peptide (AIP) signal mols. were sought. A series of analogs (including the L-alanine and D-amino acid scanned peptides) was synthesized to det. the functionally crit. residues within the S. aureus group I AIP. As a consequence, it was established that (i) the group I AIP is inactivated in culture supernatants by the formation of the corresponding methionyl sulfoxide; and (ii) the group I AIP lactam analog retains the capacity to activate agr, suggesting that covalent modification of the AgrC receptor is not a necessary prerequisite for agr activation. Although each of the D-amino acid scanned AIP analogs retained activity, replacement of the endocyclic amino acid residue (aspartate) located C-terminally to the central cysteine with alanine converted the group I AIP from an activator to a potent inhibitor. The screening of clin. S. aureus isolates for novel AIP groups revealed a variant that differed from the group I AIP by a single amino acid residue (aspartate to tyrosine) in the same position defined as crit. by alanine scanning. Although this AIP inhibits group I S. aureus strains, the producer strains possess a functional agr locus dependent on the endogenous peptide and, as such, constitute a 4th S. aureus AIP pheromone group (group IV). The addn. of exogenous synthetic AIPs to S. aureus inhibited the prodn. of toxic shock syndrome toxin (TSST-1) and enterotoxin C3, confirming the potential of quorum-sensing blockade as a therapeutic strategy.

REFERENCE 2: 131:5532 Oligopeptides and their use as antibacterial agents against Staphylococcus strains. Bycroft, Barrie Walsham; Williams, Paul; Stewart, Gordon Sydney Anderson Birnie; Chan, Weng Choon; McDowell, Philip William; Affas, Zina Mariam (The University of Nottingham, UK). PCT Int. Appl. WO 9926968 A1 19990603, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN,

Searched by: Mary Hale 308-4258 CM-1 12D16

TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB3497 19981124. PRIORITY: GB 1997-24859 19971126.

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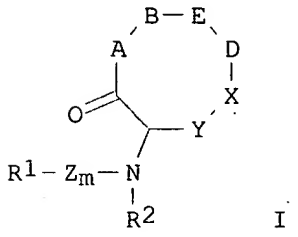

I

AB Oligopeptides I (A, B, E, D, Z are independently selected from residues of natural or synthetic amino acids or their substituted derivs.; X = S, O or NR3; Y = (CH2)n, n = 1-5, m = 0-5; R1, R2, R3 = H, alkyl, acyl, alkoxycarbonyl or, when m is zero, R1 and R2 may be linked so as to form a heterocyclic ring) or their pharmaceutically acceptable salts or prodrugs are antagonists of exotoxin prodn. or cell wall protein synthesis by bacteria such as Staphylococcus aureus and are therefore useful as antibacterial agents. Thus, cyclo(Ac-Cys-Asp-Phe-Leu-Leu), prepd. by solid-phase peptide coupling and carbodiimide-based cyclization at the Cys and Leu residues, showed an activity of 0.85 for inhibition of .beta.-lactamase activity.

L12 ANSWER 19 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 225784-72-5 REGISTRY
CN L-Leucine, N-acetyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-leucyl-, (5.fwdarw.1)-thiolactone (9CI) (CA INDEX NAME)
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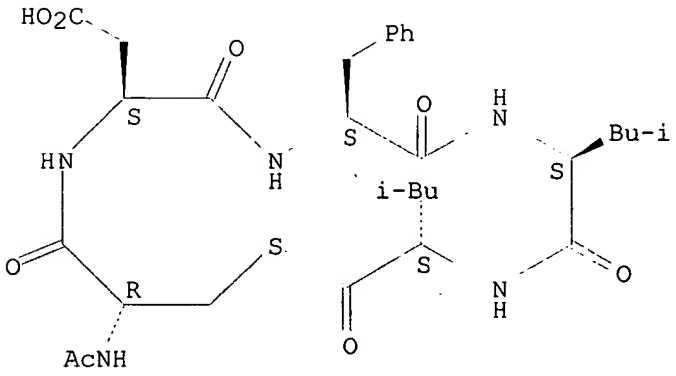
MF C30 H43 N5 O8 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
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REFERENCE 1: 131:5532 Oligopeptides and their use as antibacterial agents against Staphylococcus strains. Bycroft, Barrie Walsham; Williams, Paul; Stewart, Gordon Sydney Anderson Birnie; Chan, Weng Choon; McDowell, Philip William; Affas, Zina Mariam (The University of Nottingham, UK). PCT Int. Appl. WO 9926968 A1 19990603, 33 pp. DESIGNATED STATES: W: AL, AM, AT,

Searched by: Mary Hale 308-4258 CM-1 12D16

AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB3497 19981124. PRIORITY: GB 1997-24859 19971126.

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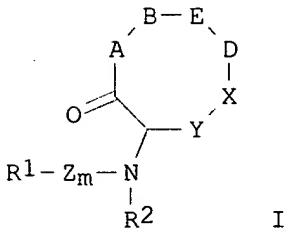

I

AB Oligopeptides I (A, B, E, D, Z are independently selected from residues of natural or synthetic amino acids or their substituted derivs.; X = S, O or NR3; Y = (CH2)n, n = 1-5, m = 0-5; R1, R2, R3 = H, alkyl, acyl, alkoxycarbonyl or, when m is zero, R1 and R2 may be linked so as to form a heterocyclic ring) or their pharmaceutically acceptable salts or prodrugs are antagonists of exotoxin prodn. or cell wall protein synthesis by bacteria such as Staphylococcus aureus and are therefore useful as antibacterial agents. Thus, cyclo(Ac-Cys-Asp-Phe-Leu-Leu), prepd. by solid-phase peptide coupling and carbodiimide-based cyclization at the Cys and Leu residues, showed an activity of 0.85 for inhibition of .beta.-lactamase activity.

L12 ANSWER 20 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 223271-99-6 REGISTRY
CN L-Phenylalanine, glycyl-L-valyl-L-asparaginyl-L-alanyl-L-seryl-L-seryl-L-seryl-L-leucyl-, (9.fwdarw.5)-lactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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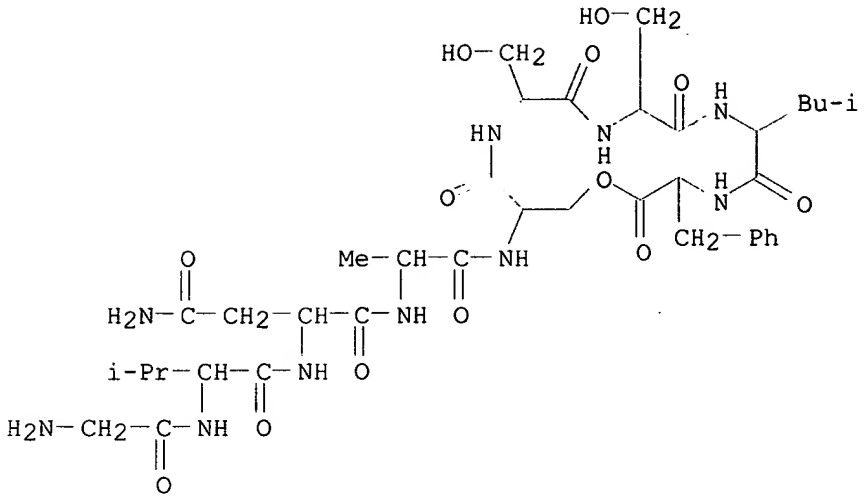
LC STN Files: CA, CAPLUS, USPATFULL

Searched by: Mary Hale 308-4258 CM-1 12D16



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:101248 Staphylococcus peptides for bacterial interference. Muir, Tom W.; Mayville, Patricia; Novick, Richard P.; Beavis, Ronald; Ji, Guangyong (Rockefeller University, USA; New York University). U.S. US 6337385 B1 20020108, 18 pp. (English). CODEN: USXXAM. APPLICATION: US 1999-339511 19990624. PRIORITY: US 1998-PV90402 19980624.

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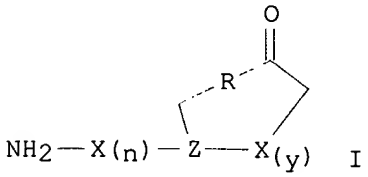

AB The present invention provides a cyclic peptide comprising the structure NH2-X(n) -Z-X(y) -COOH where X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The present invention also provides a cyclic peptide comprising the amino acid sequence of NH2-X(n) -Z-X(y) -COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10. Methods of prepn. including a cyclization protocol, and methods of use of the cyclic peptides of the invention are also disclosed. Specifically, cyclic peptides were synthesized which interfere with the binding of the Staphylococcus aureus virulence factor AgrD with the AgrC receptor which is a step in the agr response.

REFERENCE 2: 130:293868 Structure-activity analysis of synthetic autoinducing thiolactone peptides from Staphylococcus aureus responsible for virulence. Mayville, Patricia; Ji, Guangyong; Beavis, Ronald; Yang,

Searched by: Mary Hale 308-4258 CM-1 12D16

Hongmei; Goger, Michael; Novick, Richard P.; Muir, Tom W. (Laboratory of Synthetic Protein Chemistry, The Rockefeller University, New York, NY, 10021, USA). Proc. Natl. Acad. Sci. U. S. A., 96(4), 1218-1223 (English) 1999. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB The synthesis of virulence factors and other extracellular proteins responsible for pathogenicity in S. aureus is under the control of the agr locus. A secreted agr-encoded peptide, AgrD, processed from the AgrD gene product, is known to be an effector of self-strain activation and cross-strain inhibition of the agr response. Biochem. anal. of AgrD peptides isolated from culture supernatants has suggested that they contain an unusual thiol ester-linked cyclic structure. In the present work, chem. synthesis is used to confirm that the mature AgrD peptides contain a thiolactone structure and that this feature is absolutely necessary for full biol. activity. The AgrD synthetic thiolactone peptides exhibited biol. activity in vivo in a mouse protection test. Structure-activity studies have allowed key aspects of the peptide structure involved in the differential activation and inhibition functions to be identified. Accordingly, a model for activation and inhibition of the agr response is proposed in which the former, but not the latter, involves specific acylation of the agr transmembrane receptor, AgrC.

L12 ANSWER 21 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 200010-32-8 REGISTRY
CN L-Leucine, L-tyrosyl-L-isoleucyl-L-asparaginyl-L-cysteinyl-L-.alpha.-aspartyl-L-phenylalanyl-L-leucyl-, (8.fwdarw.4)-thiolactone (9CI) (CA INDEX NAME)
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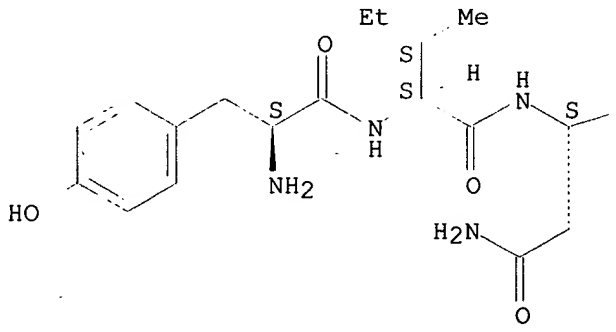
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT

Absolute stereochemistry.

PAGE 1-A



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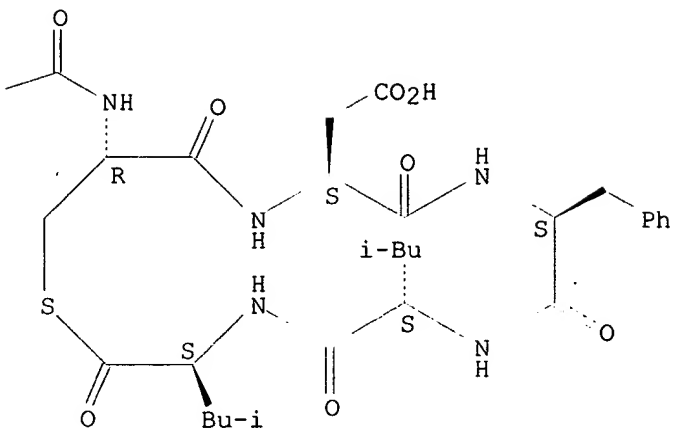
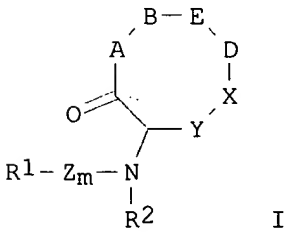


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 131:5532 Oligopeptides and their use as antibacterial agents against Staphylococcus strains. Bycroft, Barrie Walsham; Williams, Paul; Stewart, Gordon Sydney Anderson Birnie; Chan, Weng Choon; McDowell, Philip William; Affas, Zina Mariam (The University of Nottingham, UK). PCT Int. Appl. WO 9926968 A1 19990603, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB3497 19981124. PRIORITY: GB 1997-24859 19971126.

GI



I

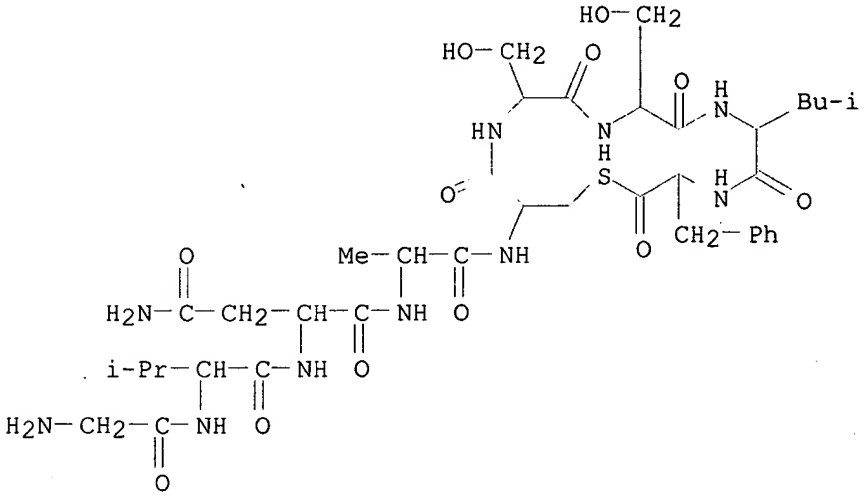
AB Oligopeptides I (A, B, E, D, Z are independently selected from residues of natural or synthetic amino acids or their substituted derivs.; X = S, O or NR3; Y = (CH2)n, n = 1-5, m = 0-5; R1, R2, R3 = H, alkyl, acyl, alkoxycarbonyl or, when m is zero, R1 and R2 may be linked so as to form a heterocyclic ring) or their pharmaceutically acceptable salts or prodrugs are antagonists of exotoxin prodn. or cell wall protein synthesis by bacteria such as Staphylococcus aureus and are therefore useful as antibacterial agents. Thus, cyclo(Ac-Cys-Asp-Phe-Leu-Leu), prepd. by solid-phase peptide coupling and carbodiimide-based cyclization at the Cys and Leu residues, showed an activity of 0.85 for inhibition of .beta.-lactamase activity.

Searched by: Mary Hale 308-4258 CM-1 12D16

REFERENCE 2: 128:43838 Blocking expression of virulence factors in Staphylococcus aureus with AgrD-derived peptides. Novick, Richard P.; Ji, Guangyong; Beavis, Ronald (New York University, USA). PCT Int. Appl. WO 9744349 A1 19971127, 23 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US8791 19970522. PRIORITY: US 1996-651226 19960522.

AB This invention provides peptides which inhibit agr-RNAIII transcription in S. aureus and thereby block the expression of virulence factors, pharmaceutical compns. comprising these peptides, as well as methods for treating or preventing an infection or disease caused by S. aureus using the peptides of the present invention. Cyclic peptides derived from gene agrD protein of one strain of S. aureus were shown to activate or inhibit the transcription of the agr-RNAIII gene in other S. aureus strains. The corresponding cyclic peptide from S. lugdunensis had similar activities.

L12 ANSWER 22 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 200010-31-7 REGISTRY
CN L-Phenylalanine, glycyl-L-valyl-L-asparaginyl-L-alanyl-L-cysteinyl-L-seryl-L-seryl-L-leucyl-, (9.fwdarw.5)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C38 H58 N10 O12 S
SR CA
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT, USPATFULL

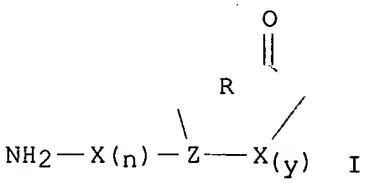


4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:101248 Staphylococcus peptides for bacterial interference. Muir, Tom W.; Mayville, Patricia; Novick, Richard P.; Beavis, Ronald; Ji, Guangyong (Rockefeller University, USA; New York University). U.S. US 6337385 B1 20020108, 18 pp. (English). CODEN: USXXAM. APPLICATION: US 1999-339511 19990624. PRIORITY: US 1998-PV90402 19980624.

GI

Searched by: Mary Hale 308-4258 CM-1 12D16



I

AB The present invention provides a cyclic peptide comprising the structure NH2-X(n) -Z-X(y) -COOH where X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The present invention also provides a cyclic peptide comprising the amino acid sequence of NH2-X(n) -Z-X(y) -COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10. Methods of prepn. including a cyclization protocol, and methods of use of the cyclic peptides of the invention are also disclosed. Specifically, cyclic peptides were synthesized which interfere with the binding of the Staphylococcus aureus virulence factor AgrD with the AgrC receptor which is a step in the agr response.

REFERENCE 2: 135:369161 Compounds and methods for regulating bacterial growth and pathogenesis. Bassler, Bonnie L.; Dammel, Carol S.; Schauder, Stephan; Shokat, Kevan; Stein, Jeffrey; Surette, Michael G. (Princeton University, USA; Quorex Pharmaceuticals, Inc.; University Technologies International, Inc.). PCT Int. Appl. WO 2001085664 A2 20011115, 134 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US15221 20010510. PRIORITY: US 2000-PV203000 20000510; US 2000-PV254398 20001207.

AB The invention provides autoinducer-2 analogs that regulate the activity of autoinducer-2 and methods of using such analogs for regulating bacterial growth and pathogenesis.

REFERENCE 3: 130:293868 Structure-activity analysis of synthetic autoinducing thiolactone peptides from Staphylococcus aureus responsible for virulence. Mayville, Patricia; Ji, Guangyong; Beavis, Ronald; Yang, Hongmei; Goger, Michael; Novick, Richard P.; Muir, Tom W. (Laboratory of Synthetic Protein Chemistry, The Rockefeller University, New York, NY, 10021, USA). Proc. Natl. Acad. Sci. U. S. A., 96(4), 1218-1223 (English) 1999. CODEN: PNASA6. ISSN: 0027-8424. Publisher: National Academy of Sciences.

AB The synthesis of virulence factors and other extracellular proteins responsible for pathogenicity in S. aureus is under the control of the agr locus. A secreted agr-encoded peptide, AgrD, processed from the AgrD gene product, is known to be an effector of self-strain activation and cross-strain inhibition of the agr response. Biochem. anal. of AgrD peptides isolated from culture supernatants has suggested that they contain an unusual thiol ester-linked cyclic structure. In the present

work, chem. synthesis is used to confirm that the mature AgrD peptides contain a thiolactone structure and that this feature is absolutely necessary for full biol. activity. The AgrD synthetic thiolactone peptides exhibited biol. activity in vivo in a mouse protection test. Structure-activity studies have allowed key aspects of the peptide structure involved in the differential activation and inhibition functions to be identified. Accordingly, a model for activation and inhibition of the agr response is proposed in which the former, but not the latter, involves specific acylation of the agr transmembrane receptor, AgrC.

REFERENCE 4: 128:43838 Blocking expression of virulence factors in Staphylococcus aureus with AgrD-derived peptides. Novick, Richard P.; Ji, Guangyong; Beavis, Ronald (New York University, USA). PCT Int. Appl. WO 9744349 A1 19971127, 23 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US8791 19970522. PRIORITY: US 1996-651226 19960522.

AB This invention provides peptides which inhibit agr-RNAIII transcription in S. aureus and thereby block the expression of virulence factors, pharmaceutical compns. comprising these peptides, as well as methods for treating or preventing an infection or disease caused by S. aureus using the peptides of the present invention. Cyclic peptides derived from gene agrD protein of one strain of S. aureus were shown to activate or inhibit the transcription of the agr-RNAIII gene in other S. aureus strains. The corresponding cyclic peptide from S. lugdunensis had similar activities.

L12 ANSWER 23 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 200010-29-3 REGISTRY
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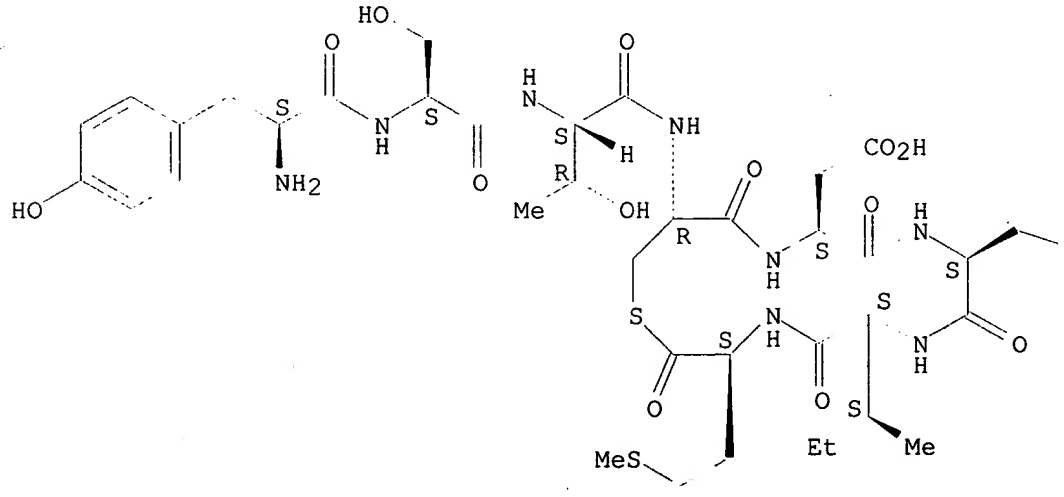
LC STN Files: CA, CAPLUS, TOXCENTER, TOXLIT, USPATFULL

Absolute stereochemistry.

PAGE 1-A



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Ph

5 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 136:101248 Staphylococcus peptides for bacterial interference. Muir, Tom W.; Mayville, Patricia; Novick, Richard P.; Beavis, Ronald; Ji, Guangyong (Rockefeller University, USA; New York University). U.S. US 6337385 B1 20020108, 18 pp. (English). CODEN: USXXAM. APPLICATION: US 1999-339511 19990624. PRIORITY: US 1998-PV90402 19980624.

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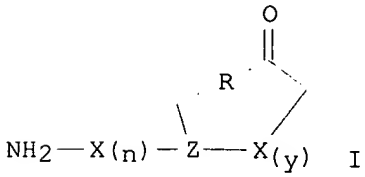

I

AB The present invention provides a cyclic peptide comprising the structure NH2-X(n) -Z-X(y) -COOH where X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, R is selected from the group consisting of oxygen, nitrogen, sulfur and carbon, n is 0 to 10 and y is 1 to 10. The present invention also provides a cyclic peptide comprising the amino acid sequence of NH2-X(n) -Z-X(y) -COOH and a cyclic bond between the Z residue and COOH other than a thioester bond, wherein X is selected from the group consisting of an amino acid, an amino acid analog, a peptidomimetic and a non-amide isostere, Z is selected from the group consisting of a synthetic amino acid and a biosynthetic amino acid, n is 0 to 10 and y is 1 to 10. Methods of prepn. including a cyclization protocol, and methods of use of the cyclic peptides of the invention are also disclosed. Specifically, cyclic peptides were synthesized which interfere with the binding of the Staphylococcus aureus virulence factor AgrD with the AgrC receptor which is a step in the agr response.

REFERENCE 2: 135:369161 Compounds and methods for regulating bacterial growth and pathogenesis. Bassler, Bonnie L.; Dammel, Carol S.; Schauder, Stephan; Shokat, Kevan; Stein, Jeffrey; Surette, Michael G. (Princeton University, USA; Quorex Pharmaceuticals, Inc.; University Technologies International, Inc.). PCT Int. Appl. WO 2001085664 A2 20011115, 134 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL,

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AB The invention provides autoinducer-2 analogs that regulate the activity of autoinducer-2 and methods of using such analogs for regulating bacterial growth and pathogenesis.

REFERENCE 3: 135:300787 Structure, activity and evolution of the group I thiolactone peptide quorum-sensing system of Staphylococcus aureus. McDowell, Philip; Affas, Zina; Reynolds, Caroline; Holden, Matthew T. G.; Wood, Stewart J.; Saint, Sandra; Cockayne, Alan; Hill, Philip J.; Dodd, Christine E. R.; Bycroft, Barrie W.; Chan, Weng C.; Williams, Paul (Inst. Infections Immunity, Univ. Nottingham, Nottingham, NG7 2RD, UK). Molecular Microbiology, 41(2), 503-512 (English) 2001. CODEN: MOMIEE. ISSN: 0950-382X. Publisher: Blackwell Science Ltd..

AB In S. aureus, the agr locus is responsible for controlling virulence gene expression via quorum sensing. As the blockade of quorum sensing offers a novel strategy for attenuating infection, novel insights into the structure, activity and turnover of the secreted staphylococcal auto-inducing peptide (AIP) signal mols. were sought. A series of analogs (including the L-alanine and D-amino acid scanned peptides) was synthesized to det. the functionally crit. residues within the S. aureus group I AIP. As a consequence, it was established that (i) the group I AIP is inactivated in culture supernatants by the formation of the corresponding methionyl sulfoxide; and (ii) the group I AIP lactam analog retains the capacity to activate agr, suggesting that covalent modification of the AgrC receptor is not a necessary prerequisite for agr activation. Although each of the D-amino acid scanned AIP analogs retained activity, replacement of the endocyclic amino acid residue (aspartate) located C-terminally to the central cysteine with alanine converted the group I AIP from an activator to a potent inhibitor. The screening of clin. S. aureus isolates for novel AIP groups revealed a variant that differed from the group I AIP by a single amino acid residue (aspartate to tyrosine) in the same position defined as crit. by alanine scanning. Although this AIP inhibits group I S. aureus strains, the producer strains possess a functional agr locus dependent on the endogenous peptide and, as such, constitute a 4th S. aureus AIP pheromone group (group IV). The addn. of exogenous synthetic AIPs to S. aureus inhibited the prodn. of toxic shock syndrome toxin (TSST-1) and enterotoxin C3, confirming the potential of quorum-sensing blockade as a therapeutic strategy.

REFERENCE 4: 131:5532 Oligopeptides and their use as antibacterial agents against Staphylococcus strains. Bycroft, Barrie Walsham; Williams, Paul; Stewart, Gordon Sydney Anderson Birnie; Chan, Weng Choon; McDowell, Philip William; Affas, Zina Mariam (The University of Nottingham, UK). PCT Int. Appl. WO 9926968 A1 19990603, 33 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1998-GB3497 19981124. PRIORITY: GB 1997-24859 19971126.

GI

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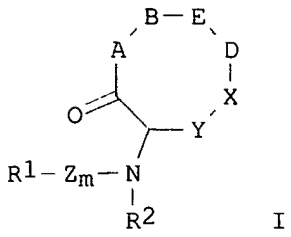

I

AB Oligopeptides I (A, B, E, D, Z are independently selected from residues of natural or synthetic amino acids or their substituted derivs.; X = S, O or NR3; Y = (CH2)n, n = 1-5, m = 0-5; R1, R2, R3 = H, alkyl, acyl, alkoxycarbonyl or, when m is zero, R1 and R2 may be linked so as to form a heterocyclic ring) or their pharmaceutically acceptable salts or prodrugs are antagonists of exotoxin prodn. or cell wall protein synthesis by bacteria such as Staphylococcus aureus and are therefore useful as antibacterial agents. Thus, cyclo(Ac-Cys-Asp-Phe-Leu-Leu), prepd. by solid-phase peptide coupling and carbodiimide-based cyclization at the Cys and Leu residues, showed an activity of 0.85 for inhibition of .beta.-lactamase activity.

REFERENCE 5: 128:43838 Blocking expression of virulence factors in Staphylococcus aureus with AgrD-derived peptides. Novick, Richard P.; Ji, Guangyong; Beavis, Ronald (New York University, USA). PCT Int. Appl. WO 9744349 A1 19971127, 23 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US8791 19970522. PRIORITY: US 1996-651226 19960522.

AB This invention provides peptides which inhibit agr-RNAIII transcription in S. aureus and thereby block the expression of virulence factors, pharmaceutical compns. comprising these peptides, as well as methods for treating or preventing an infection or disease caused by S. aureus using the peptides of the present invention. Cyclic peptides derived from gene agrD protein of one strain of S. aureus were shown to activate or inhibit the transcription of the agr-RNAIII gene in other S. aureus strains. The corresponding cyclic peptide from S. lugdunensis had similar activities.

L12 ANSWER 24 OF 25 REGISTRY COPYRIGHT 2002 ACS
RN 200010-27-1 REGISTRY
CN L-Phenylalanine, L-.alpha.-aspartyl-L-isoleucyl-L-cysteinyl-L-asparaginyl-L-alanyl-L-tyrosyl-, (7.fwdarw.3)-thiolactone (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
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SR CA
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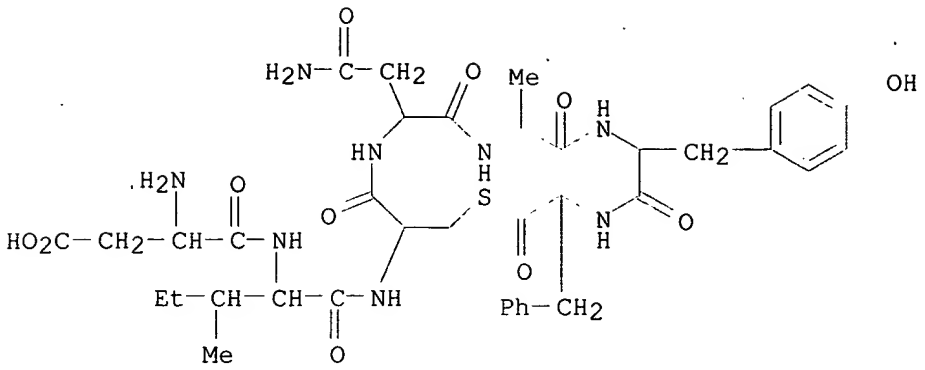

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 128:43838 Blocking expression of virulence factors in Staphylococcus aureus with AgrD-derived peptides. Novick, Richard P.; Ji, Guangyong; Beavis, Ronald (New York University, USA). PCT Int. Appl. WO 9744349 A1 19971127, 23 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US8791 19970522. PRIORITY: US 1996-651226 19960522.

AB This invention provides peptides which inhibit agr-RNAIII transcription in S. aureus and thereby block the expression of virulence factors, pharmaceutical compns. comprising these peptides, as well as methods for treating or preventing an infection or disease caused by S. aureus using the peptides of the present invention. Cyclic peptides derived from gene agrD protein of one strain of S. aureus were shown to activate or inhibit the transcription of the agr-RNAIII gene in other S. aureus strains. The corresponding cyclic peptide from S. lugdunensis had similar activities.

L12 ANSWER 25 OF 25 REGISTRY COPYRIGHT 2002 ACS
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OTHER CA INDEX NAMES:
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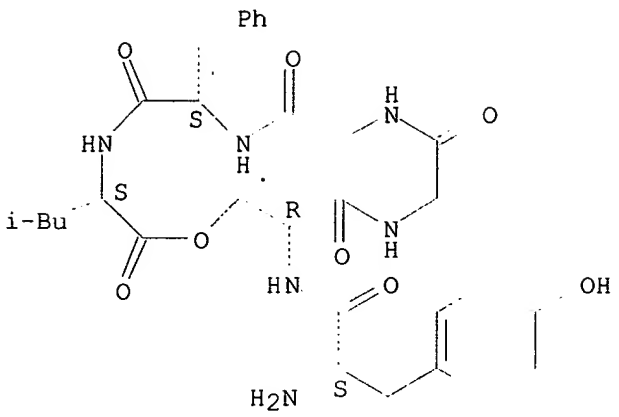
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



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1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 106:33456 Peptide conformations. 37. Synthesis and conformational studies of enkephalin-like cyclic peptides and depsipeptides. Zechel, Christian; Kessler, Horst; Geiger, Rolf (Inst. Org. Chem., Univ. Frankfurt, Frankfurt, D-6000, Fed. Rep. Ger.). Pept.: Struct. Funct., Proc. Am. Pept. Symp., 9th, 507-10 (English) 1985. CODEN: 54ZNAJ.

GI For diagram(s), see printed CA Issue.

AB Enkephalin cyclic peptide analogs I [X = Phe, MePhe, 1,2,3,4-tetrahydroisoquinolinecarboxylic acid (Tic)] and enkephalin cyclic depsipeptide analogs II (n = 1, 2) were prepd. and their conformations were studied by 1H, 13C, and 15N NMR spectroscopy. Thus, Boc-D-Ser-Gly-OCH2Ph (Boc = Me3CO2C) was O-acylated with Ddz-Leu-OH (Ddz = .alpha.,.alpha.-dimethyl-3,5-dimethoxybenzyloxycarbonyl) by PPA to give O-acylserine deriv. III (R = Odz), which was Ddz-deblocked by 3% CF3CO2H/CH2Cl2 and then coupled with Z-Phe-OH (Z = PhCH2O2C) by PPA to give III (R = Z-Phe). The latter was Z-deblocked and then cyclized by EDCI/DMAP to give peptide lactone IV, which was converted into II (n = 1). Only I (X = Phe, Tic) and II (n = 1) have homogeneous conformations; I (X = MePhe) exists in 2 conformations due to cis-trans isomerization at the Gly-MePhe bond. Flexible I (X = MePhe) exhibited the highest activity in the guinea pig ileum assay, whereas rigid I (X = Phe) was less potent. The potency drops further in the most rigid I (Tic).

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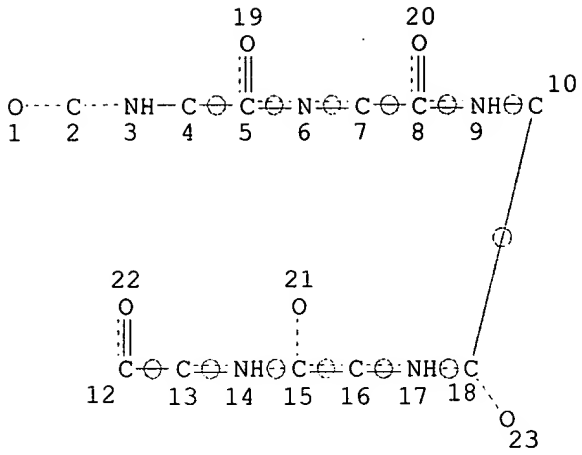

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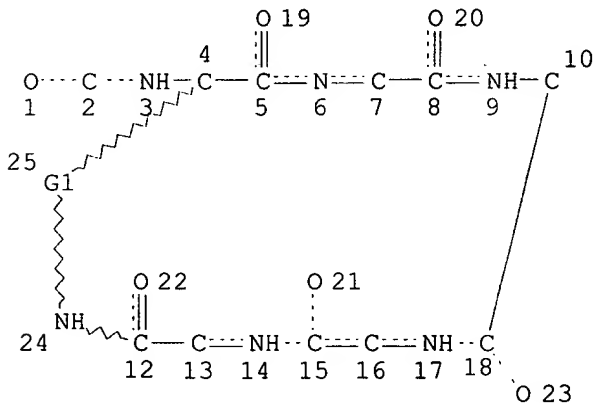

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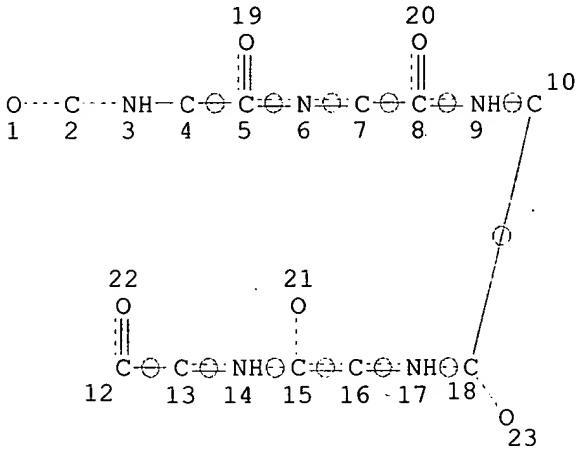

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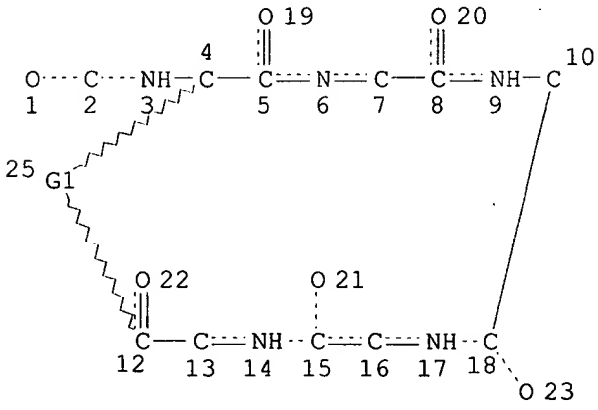

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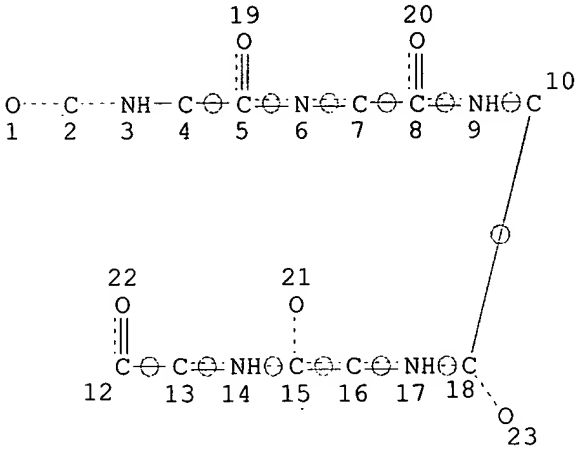

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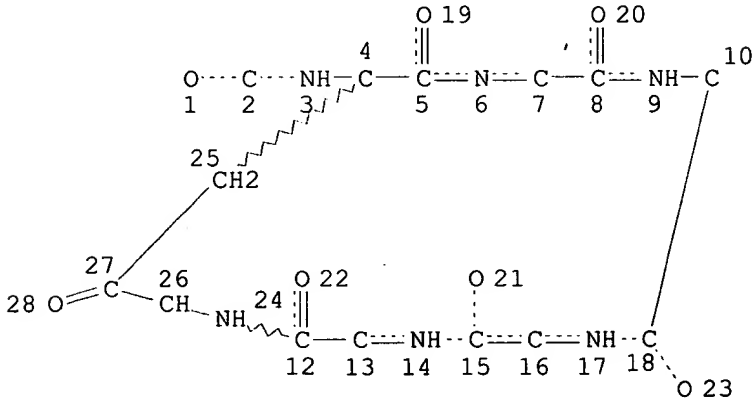

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FULL ESTIMATED COST                               517.20     727.60

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FILE 'EMBASE' ENTERED AT 10:01:13 ON 12 MAR 2002
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FILE 'JICST-EPLUS' ENTERED AT 10:01:13 ON 12 MAR 2002
COPYRIGHT (C) 2002 Japan Science and Technology Corporation (JST)


L17          578 FILE MEDLINE
L18          464 FILE CAPLUS
L19          319 FILE BIOSIS


Searched by: Mary Hale 308-4258 CM-1 12D16
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L20          753 FILE EMBASE
L21            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L22         2114 L10 OR L12

=> s l22 and antagonist and g protein couple?
L23            0 FILE MEDLINE
L24            3 FILE CAPLUS
L25            0 FILE BIOSIS
L26            0 FILE EMBASE
L27            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L28            3 L22 AND ANTAGONIST AND G PROTEIN COUPLE?

=> s l22 and c5a receptor
L29            0 FILE MEDLINE
L30            9 FILE CAPLUS
L31            0 FILE BIOSIS
L32            0 FILE EMBASE
L33            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L34            9 L22 AND C5A RECEPTOR

=> s l28 or l34
L35            0 FILE MEDLINE
L36           10 FILE CAPLUS
L37            0 FILE BIOSIS
L38            0 FILE EMBASE
L39            0 FILE JICST-EPLUS

TOTAL FOR ALL FILES
L40           10 L28 OR L34

=> dup rem l40
PROCESSING COMPLETED FOR L40
L41            10 DUP REM L40 (0 DUPLICATES REMOVED)

=> d 1-10 cbib abs hitstr

L41  ANSWER 1 OF 10  CAPLUS  COPYRIGHT 2002 ACS
2001:329752   Document No. 135:117301  Structure-activity relationship studies
      of melanin-concentrating hormone (MCH)-related peptide ligands at SLC-1,
      the human MCH receptor.  Audinot, Valerie; Beauverger, Philippe; Lahaye,
      Chantal; Suply, Thomas; Rodriguez, Marianne; Ouvry, Christine; Lamamy,
      Veronique; Imbert, Jerome; Rique, Herve; Nahon, Jean-Louis; Galizzi,
      Jean-Pierre; Canet, Emmanuel; Levens, Nigel; Fauchere, Jean-Luc; Boutin,
      Jean A. (Division de Pharmacologie Moleculaire et Cellulaire, Institut de
      Recherches SERVIER, Croissy sur Seine, 78290, Fr.).  Journal of Biological
      Chemistry, 276(17), 13554-13562 (English) 2001.  CODEN: JBCHA3.  ISSN:
      0021-9258.  Publisher: American Society for Biochemistry and Molecular
      Biology.
AB    Melanin-concg. hormone (MCH) is a cyclic nonadecapeptide involved in the
      regulation of feeding behavior, which acts through a G
      protein-coupled receptor (SLC-1) inhibiting adenyl
      cyclase activity.  In this study, 57 analogs of MCH were investigated on
      the recently cloned human MCH receptor stably expressed in HEK293 cells,
      on both the inhibition of forskolin-stimulated cAMP prodn. and
      guanosine-5'-O-3-[35S]thiotriphosphate ([35S]GTP.gamma.S) binding.  The
      dodecapeptide MCH-(6-17) (MCH ring between Cys7 and Cys16, with a single
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extra amino acid at the N terminus (Arg6) and at the C terminus (Trp17)) was found to be the minimal sequence required for a full and potent agonistic response on cAMP formation and [35S]GTP.gamma.S binding. We Ala-scanned this dodecapeptide and found that only 3 of 8 amino acids of the ring, namely Met8, Arg11, and Tyr13, were essential to elicit full and potent responses in both tests. Deletions inside the ring led either to inactivity or to poor **antagonists** with potencies in the micromolar range. Cys7 and Cys16 were substituted by Asp and Lys or one of their analogs, in an attempt to replace the disulfide bridge by an amide bond. However, those modifications were deleterious for agonistic activity. In [35S]GTP.gamma.S binding, these compds. behaved as weak **antagonists** (KB 1-4 .mu.M). Finally, substitution in MCH-(6-17) of 6 out of 12 amino acids by non-natural residues and concomitant replacement of the disulfide bond by an amide bond led to three compds. with potent antagonistic properties (KB = 0.1-0.2 .mu.M). Exploitation of these structure-activity relationships should open the way to the design of short and stable MCH peptide **antagonists**.

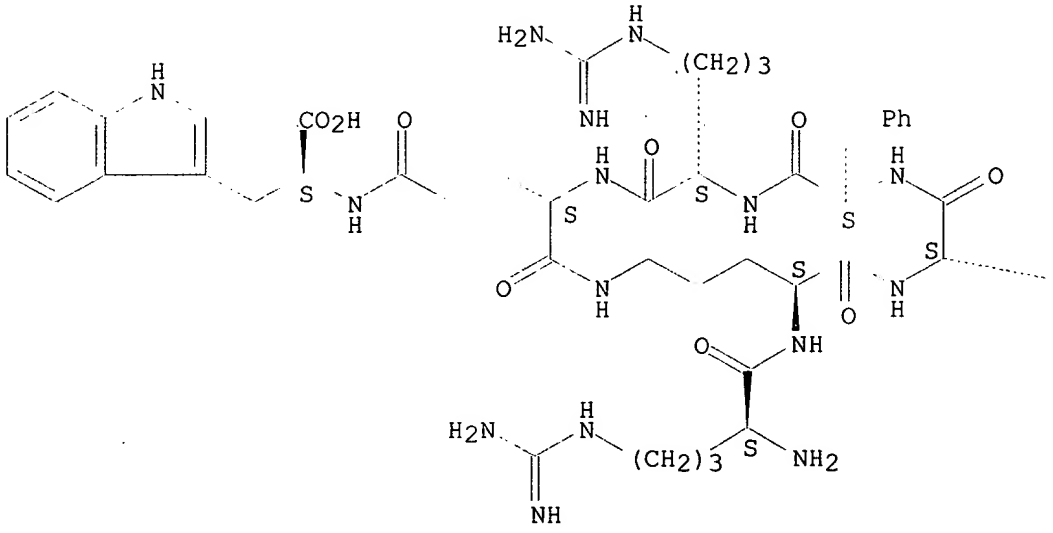
IT **350849-88-6**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(melanin-concg. hormone-related peptide ligand structure-activity relationships at human melanin-concg. hormone receptor SLC-1)

RN 350849-88-6 CAPLUS

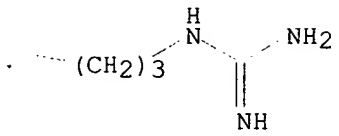
CN L-Tryptophan, L-arginyl-L-ornithyl-L-arginyl-L-phenylalanyl-L-arginyl-L-.gamma.-glutamyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16



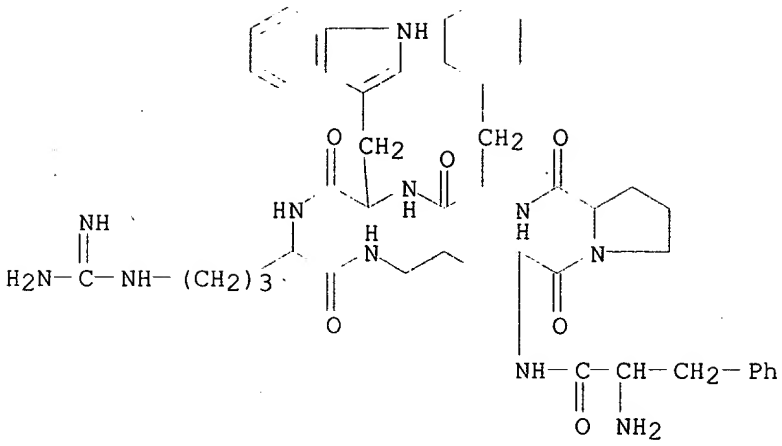
L41 ANSWER 2 OF 10 CAPLUS COPYRIGHT 2002 ACS
2001:373840 Document No. 135:179416 Modulation of ligand selectivity by mutation of the first extracellular loop of the human **C5a receptor**. Cain, S. A.; Woodruff, T. M.; Taylor, S. M.; Fairlie, D. P.; Sanderson, S. D.; Monk, P. N. (Division of Clinical Sciences, Section of Neurology, University of Sheffield Medical School, Sheffield, S10 2RX, UK). Biochem. Pharmacol., 61(12), 1571-1579 (English) 2001. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

AB The cyclic **C5a receptor** antagonist, phenylalanine [L-ornithine-proline-D-cyclohexylalanine-tryptophan-arginine] (F-[OPchaWR]), has .apprx.1000-fold less affinity for the **C5a receptor** (C5aR) on murine polymorphonuclear leukocytes than on human. Anal. of C5aR from different species shows that a possible cause of this difference is the variation in the sequence of the first extracellular loop of the receptor. The mouse receptor contains Y at a position analogous to P103 in the human receptor, and D at G105. To test this hypothesis, the authors expressed human C5aR mutants (P103Y, G105D and the double mutant, P103Y/G105D) in RBL-2H3 cells and investigated the effects of these mutations on binding affinity and receptor activation. All three mutant receptors had a higher affinity for human C5a than the wild-type receptor, but showed no significant difference in the ability of F-[OPchaWR] to inhibit human C5a binding. However, all of the mutant receptors had substantially lower affinities for the weak agonist, C5a des Arg74 (C5adR74), and two altered receptors (G105D and P103Y/G105D) had much lower affinities for the C-terminal C5a agonist peptide analog, L-tyrosine-serine-phenylalanine-lysine-proline-methionine-proline-leucine-D-alanine-arginine (YSFKPMPLaR). Although it is unlikely that differences at these residues are responsible for variations in the potency of F-[OPchaWR] across species, residues in the first extracellular loop are clearly involved in the recognition of both C5a and C5a agonists. The complex effects of mutating these residues on the affinity and response to C5a, C5adR74, and the peptide analogs provide evidence of different binding modes for these ligands on the C5aR.

IT **219639-88-0**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(role of first extracellular loop of human **C5a receptor** in ligand specificity for)

RN 219639-88-0 CAPLUS
CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Searched by: Mary Hale 308-4258 CM-1 12D16



L41 ANSWER 3 OF 10 CAPLUS COPYRIGHT 2002 ACS

2001:474758 Document No. 136:165721 Species dependence for binding of small molecule agonist and antagonists to the **C5a receptor** on polymorphonuclear leukocytes. Woodruff, Trent M.; Strachan, Anna J.; Sanderson, Sam D.; Monk, Peter N.; Wong, Allan K.; Fairlie, David P.; Taylor, Stephen M. (Department of Physiology and Pharmacology, University of Queensland, Australia). Inflammation (New York, NY, United States), 25(3), 171-177 (English) 2001. CODEN: INFLD4. ISSN: 0360-3997. Publisher: Kluwer Academic/Plenum Publishers.

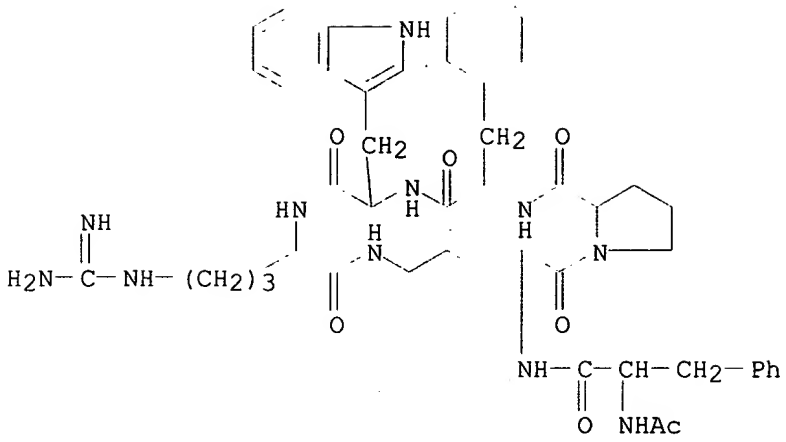
AB This study investigated the receptor binding affinities of a C5a agonist and cyclic antagonists for polymorphonuclear leukocytes (PMNs) isolated from human, sheep, pig, dog, rabbit, guinea pig, rat and mouse. The affinities of the two small mol. antagonists, F-[OPdChaWR] and AcF-[OPdChaWR], and the agonist, YSFKPMPLaR, revealed large differences in **C5a receptor** (C5aR) affinities between species. The antagonists bound to human, rat and dog PMNs with similar high affinities, but with lower affinities to PMNs from all other species. The C5a agonist also bound with varying affinities between species, but showed a different affinity profile to the antagonists. In contrast, recombinant human C5a had similar affinity for PMNs of all species investigated. The low correlation between the affinities of the antagonists and the agonist between species either suggests that different receptor residues are important for distinguishing between agonist/antagonist binding, or that the agonist and antagonist peptides bind to two distinct sites within the C5aR.

IT **219639-75-5 219639-88-0**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(species dependence for binding of small mol. agonist and antagonists to the **C5a receptor** on polymorphonuclear leukocytes)

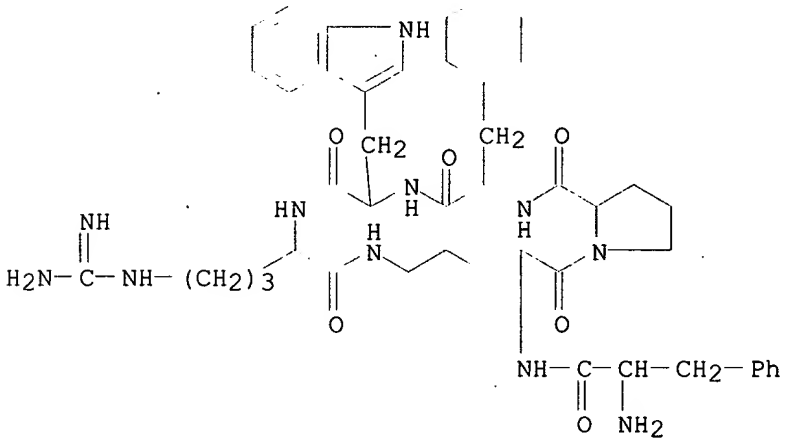
RN 219639-75-5 CAPLUS

CN L-Arginine, N-acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Searched by: Mary Hale 308-4258 CM-1 12D16



RN 219639-88-0 CAPLUS
CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



L41 ANSWER 4 OF 10 CAPLUS COPYRIGHT 2002 ACS
2000:411681 Document No. 133:148913 A new small molecule **C5a receptor** antagonist inhibits the reverse-passive Arthus reaction and endotoxic shock in rats. Strachan, Anna J.; Woodruff, Trent M.; Haaima, Gerald; Fairlie, David P.; Taylor, Stephen M. (Department of Physiology and Pharmacology, University of Queensland, St. Lucia, 4072, Australia). J. Immunol., 164(12), 6560-6565 (English) 2000. CODEN: JOIMA3. ISSN: 0022-1767. Publisher: American Association of Immunologists.

AB C5a is implicated as a pathogenic factor in a wide range of immunoinflammatory diseases, including sepsis and immune complex disease. Agents that antagonize the effects of C5a could be useful in these diseases. We have developed some novel C5a antagonists and have detd. the acute anti-inflammatory properties of a new small mol. **C5a receptor** antagonist against C5a- and LPS-induced neutrophil adhesion and cytokine expression, as well as against some hallmarks of the reverse Arthus reaction in rats. We found that a single i.v. dose (1 mg/kg) of this antagonist inhibited both C5a- and LPS-induced neutropenia and elevated levels of circulating TNF-.alpha., as well as

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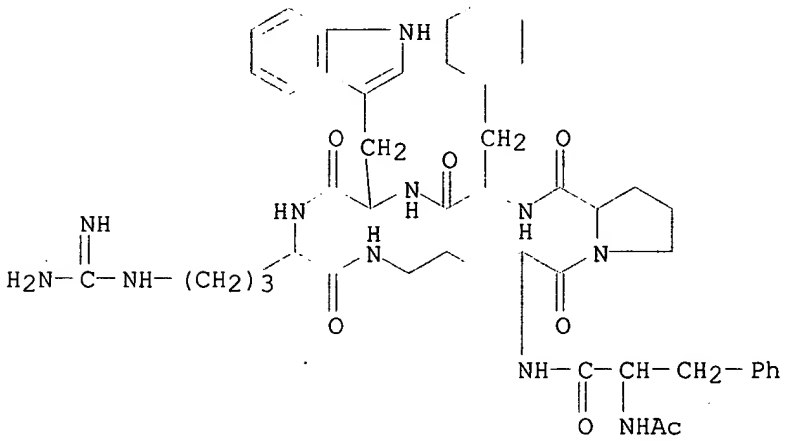
polymorphonuclear leukocyte migration, increased TNF-.alpha. levels and vascular leakage at the site of immune complex deposition. These results indicate potent anti-inflammatory activities of a new **C5a receptor** antagonist and provide more evidence for a key early role for C5a in sepsis and the reverse Arthus reaction. The results support a role for antagonists of **C5a receptors** in the therapeutic intervention of immunoinflammatory disease states such as sepsis and immune complex disease.

IT **219639-75-5**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(complement **C5a receptor** antagonist inhibits the reverse-passive Arthus reaction and endotoxic shock in rats)

RN 219639-75-5 CAPLUS

CN L-Arginine, N-acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



L41 ANSWER 5 OF 10 CAPLUS COPYRIGHT 2002 ACS

2000:526444 Document No. 133:276020 Inhibition of C5a-induced neutrophil chemotaxis and macrophage cytokine production in vitro by a new **C5a receptor** antagonist. Haynes, D. R.; Harkin, D. G.; Bignold, L. P.; Hutchens, M. J.; Taylor, S. M.; Fairlie, D. P. (Department of Pathology, University of Adelaide, Adelaide, 5005, Australia). Biochem. Pharmacol., 60(5), 729-733 (English) 2000. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc.

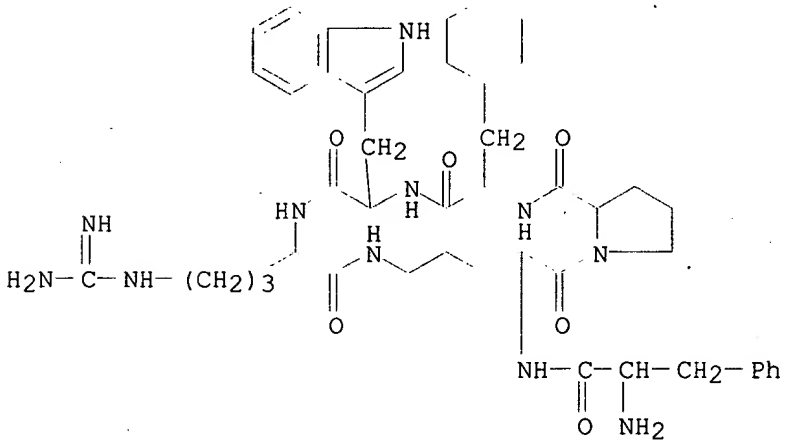
AB A cyclic peptide, Phe-[Orn-Pro-d-Cyclohexylalanine-Trp-Arg] (F-[OPdChaWR]), was recently shown in vitro to antagonize the binding of C5a to its receptor (CD88) on human polymorphonuclear leukocytes (PMNs) and in vivo to inhibit the neutropenia assocd. with septic shock induced by lipopolysaccharide (LPS) in rats. The aim of this study was to investigate whether F-[OPdChaWR] inhibits C5a-mediated chemotaxis of human PMNs using a modified Boyden chamber and C5a-stimulated release of cytokines from human monocytes in vitro. Approx. 50% of the chemotactic activity induced by 10 nM C5a was inhibited by 76 nM F-[OPdChaWR]. This correlated with inhibition of C5a-induced polarization of PMNs by F-[OPdChaWR]. C5a alone failed to induce release of the inflammatory cytokines interleukin(IL)-1.beta., tumor necrosis factor (TNF)-.alpha., and IL-6 from human monocytes at concns. up to 100 nM. However, in the presence of low concns. of LPS (50 ng/mL), both IL-1.beta. and TNF-.alpha. were stimulated by 1 nM C5a. This co-stimulation was inhibited by F-[OPdChaWR] with IC50s of 0.8 and 6.9 nM for release of TNF-.alpha. and IL-1.beta., resp. No agonist activity was detected for F-[OPdChaWR] in

either the chemotaxis or cytokine release assays at concns. up to 50 .mu.M. These results show that F-[OPdChaWR] inhibits several important inflammatory activities of C5a and suggest that **C5a receptor** antagonists may be effective in the treatment of inflammatory diseases mediated by C5a.

IT **219639-88-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of C5a-induced neutrophil chemotaxis and macrophage cytokine prodn. in vitro by a new **C5a receptor** antagonist)

RN 219639-88-0 CAPLUS

CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI). (CA INDEX NAME)



L41 ANSWER 6 OF 10 CAPLUS COPYRIGHT 2002 ACS

1999:34926 Document No. 130:105315 Cyclic agonists and **antagonists** of **C5a receptors** and **G protein-coupled** receptors. Fairlie, David; Taylor, Stephen Maxwell; Finch, Angela Monique; Wong, Allan (The University of Queensland, Australia). PCT Int. Appl. WO 9900406 A1 19990107, 80 pp. DESIGNATED STATES: W: AU, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-AU490 19980625. PRIORITY: AU 1997-7550 19970625.

AB Cyclic compds. are provided which have the ability to modulate the activity of **G protein-coupled** receptors.
The invention provides both agonists and **antagonists**. In preferred embodiments, the invention provides cyclic peptidic and cyclic or non-cyclic non-peptidic **antagonists** or agonists of C5a. The compds. of the invention are both potent and selective, and are useful in the treatment of conditions mediated by **G protein-coupled** receptors, esp. conditions mediated by overexpression or underregulation of C5a, such as a variety of inflammatory conditions.

IT **219639-70-0P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic peptidic and nonpeptidic agonists and **antagonists** of **C5a receptors** and **G protein-coupled** receptors, and therapeutic use)

RN 219639-70-0 CAPLUS

CN D-Arginine, N-acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-

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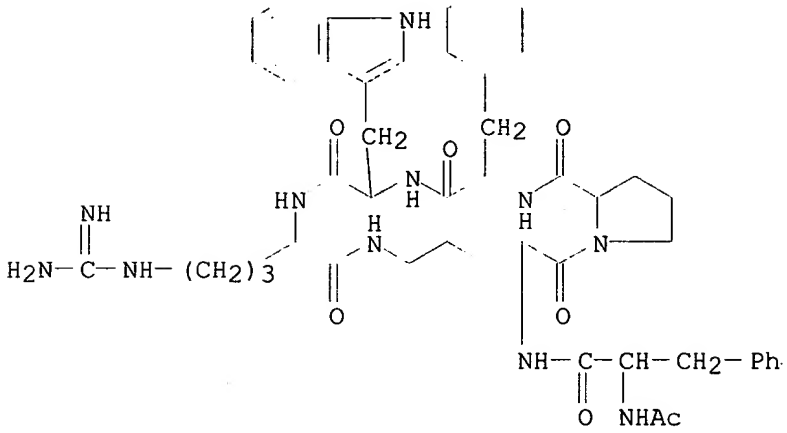
alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



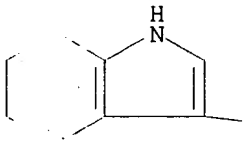
IT **219639-69-7P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic peptidic and nonpeptidic agonists and **antagonists** of **C5a receptors** and **G protein-coupled** receptors, and therapeutic use)

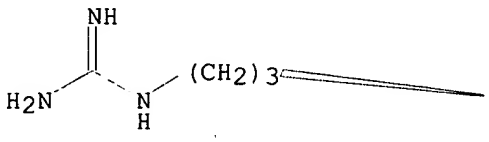
RN 219639-69-7 CAPLUS

CN D-Arginine, N-acetyl-L-phenylalanyl-L-lysyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A





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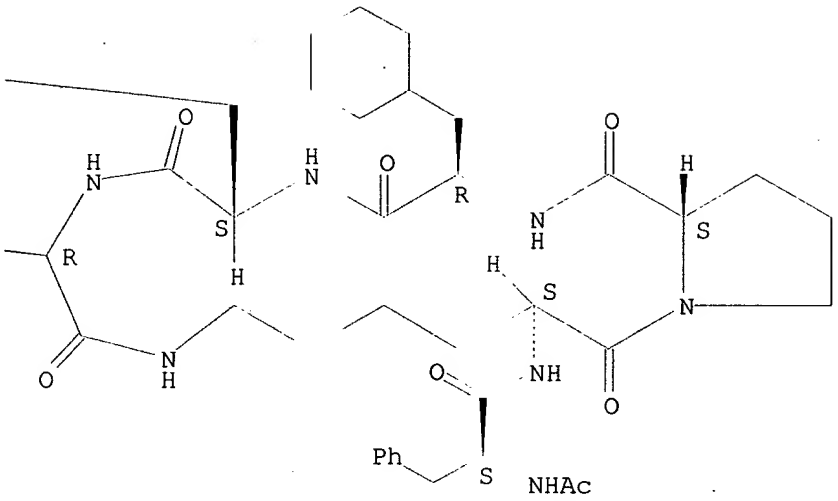

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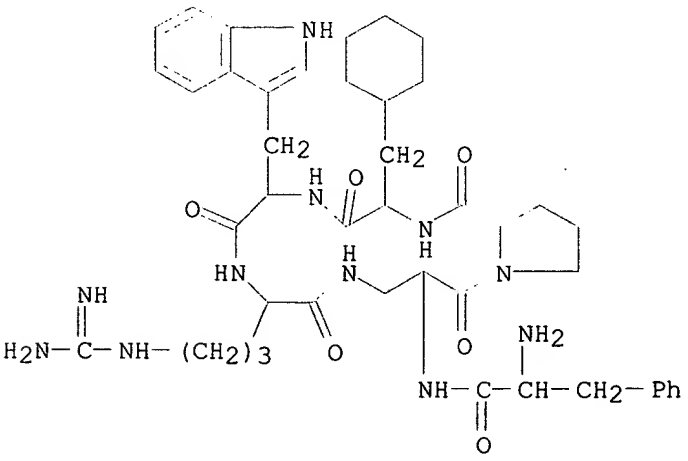
219639-81-3 219639-82-4 219639-83-5
219639-85-7 219639-88-0 219639-89-1
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic peptidic and nonpeptidic agonists and **antagonists** of **C5a receptors** and **G protein-coupled** receptors, and therapeutic use)

RN 219639-71-1 CAPLUS

CN L-Arginine, L-phenylalanyl-3-amino-L-alanyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



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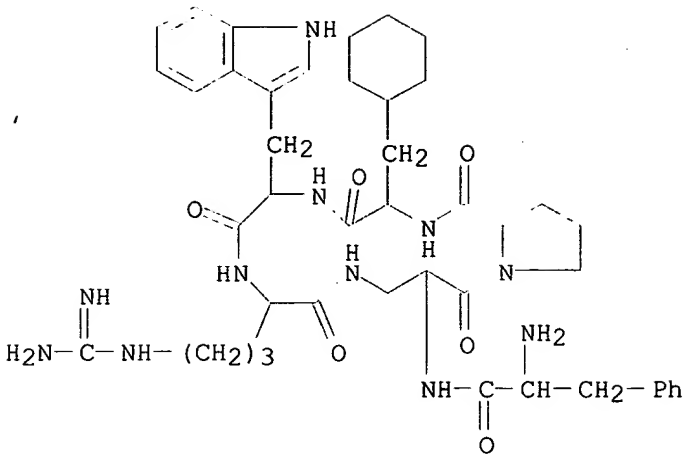
Searched by: Mary Hale 308-4258 CM-1 12D16



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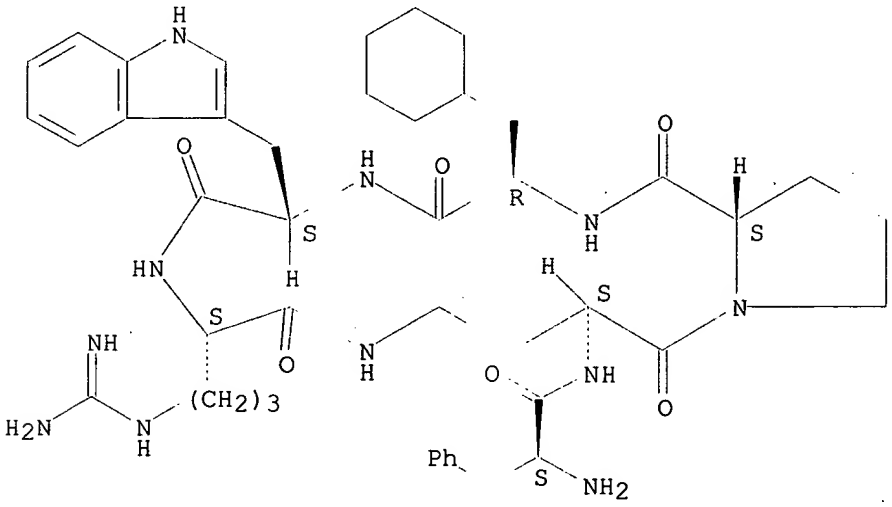
Absolute stereochemistry.



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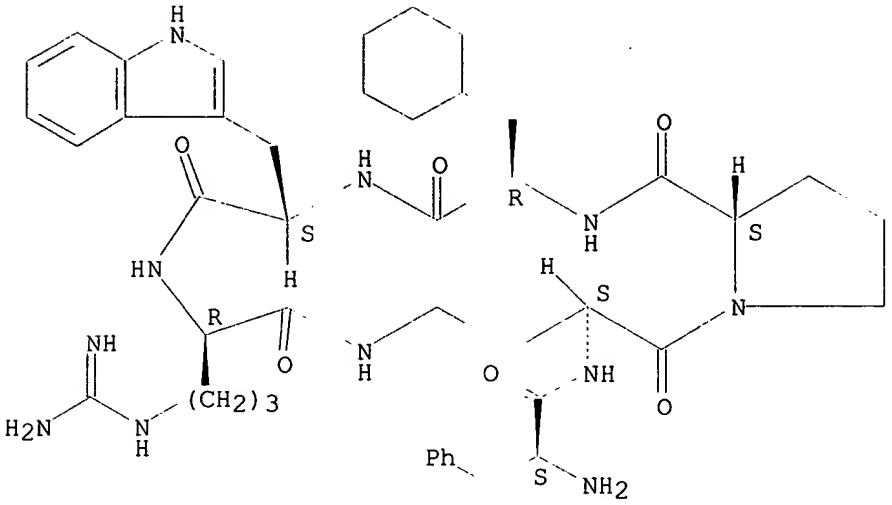
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



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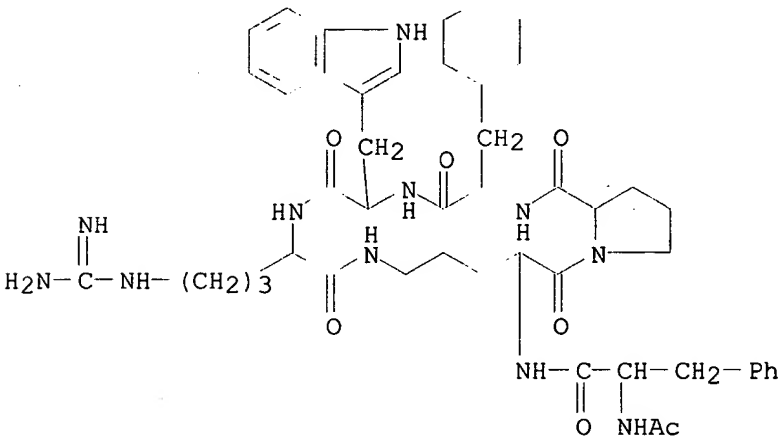

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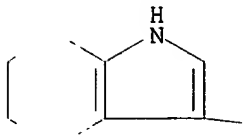
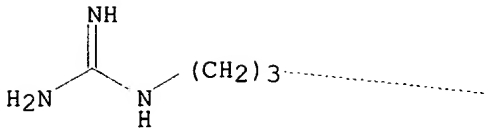
Absolute stereochemistry.

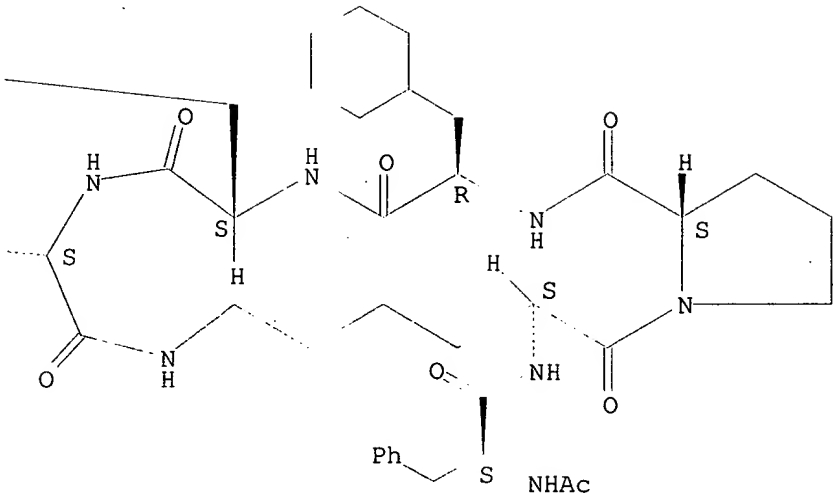
Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A





PAGE 1-B



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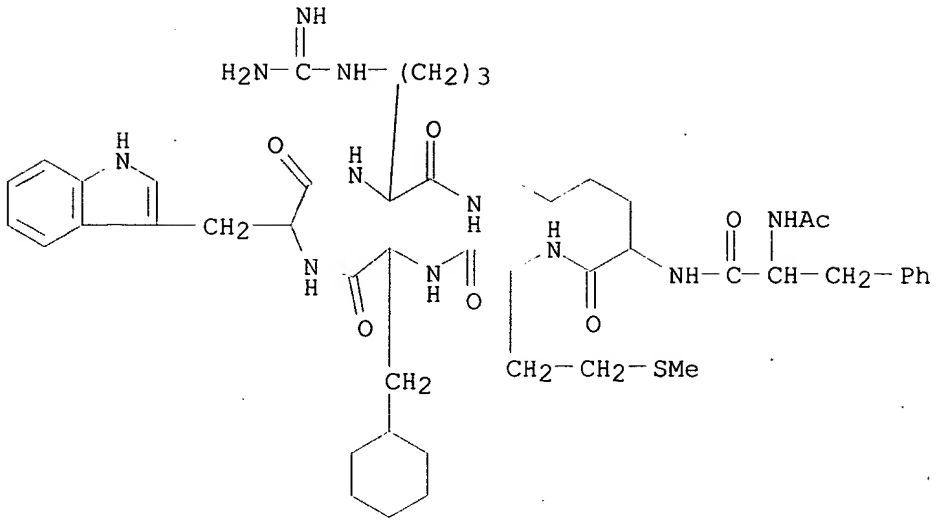
Searched by: Mary Hale 308-4258 CM-1 12D16



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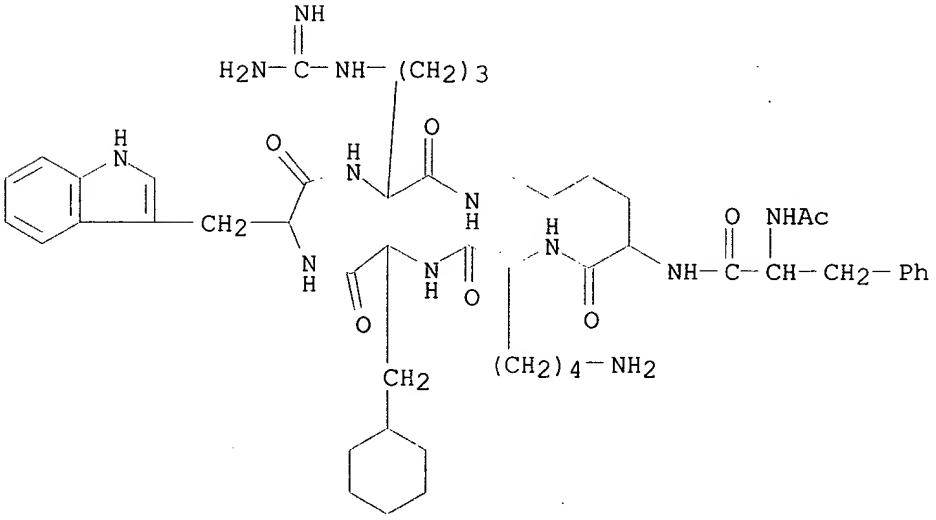

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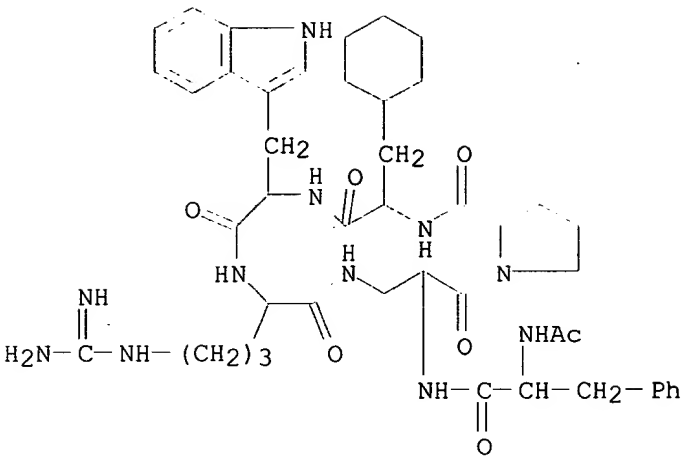
Searched by: Mary Hale 308-4258 CM-1 12D16



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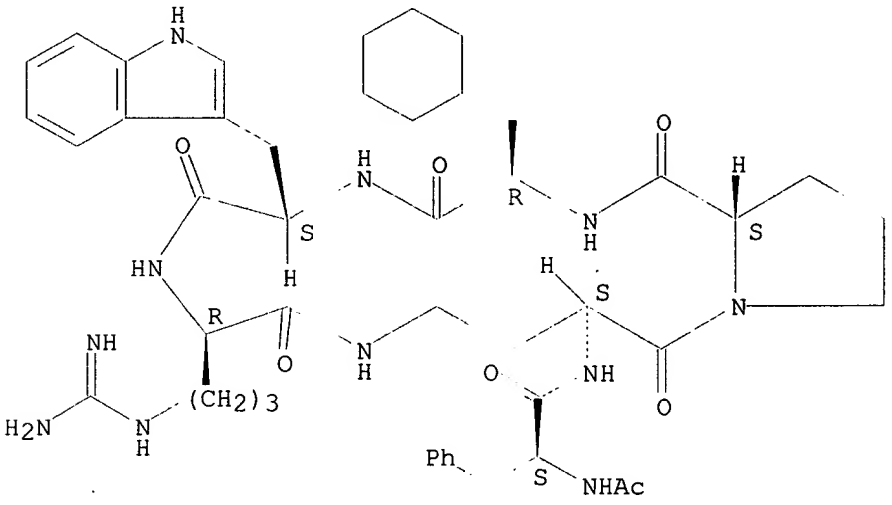
Absolute stereochemistry.



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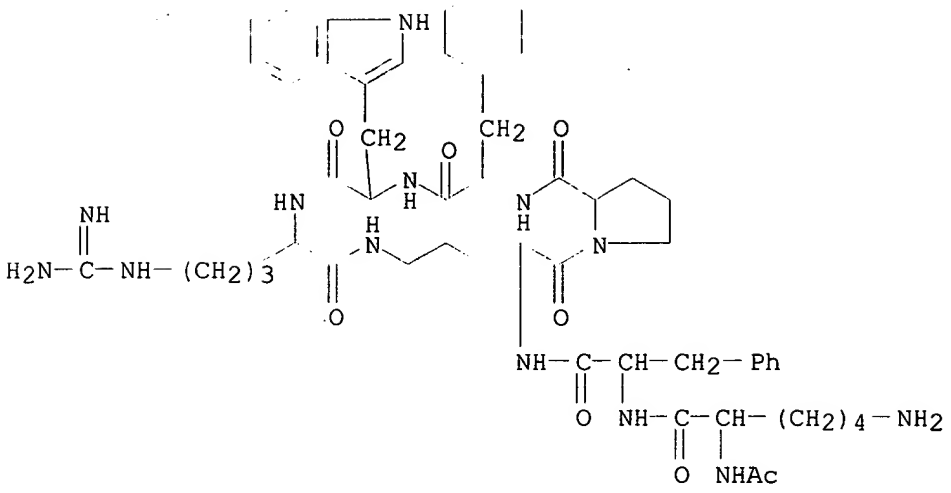
Searched by: Mary Hale 308-4258 CM-1 12D16



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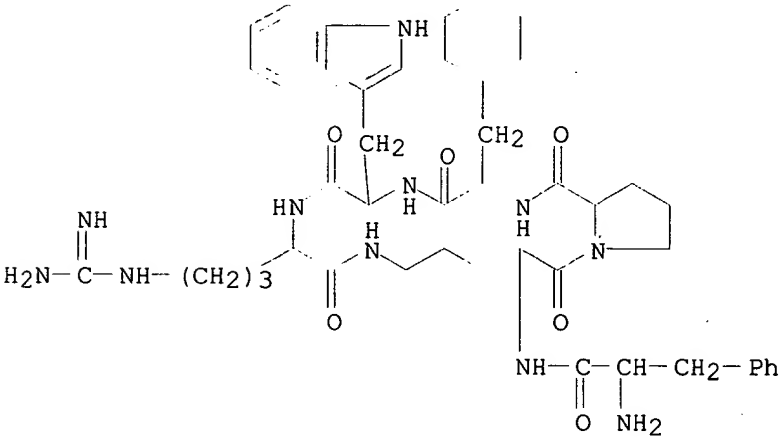

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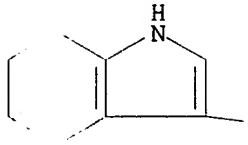
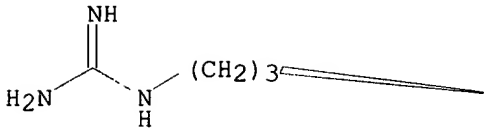
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A





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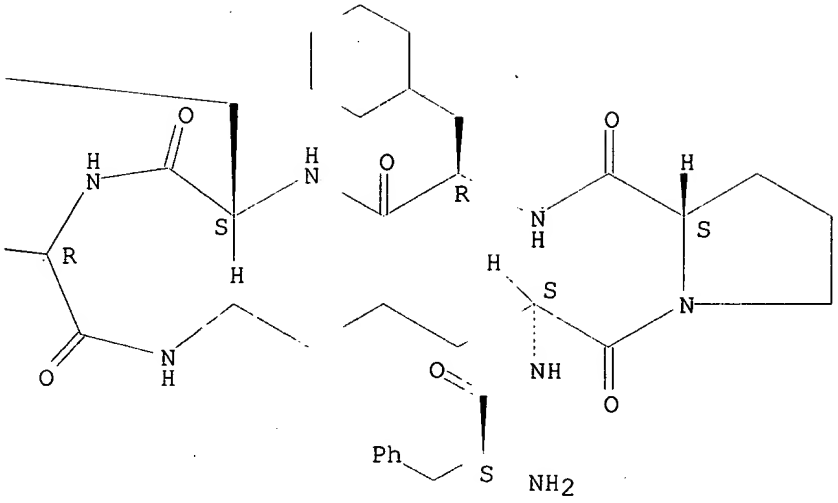

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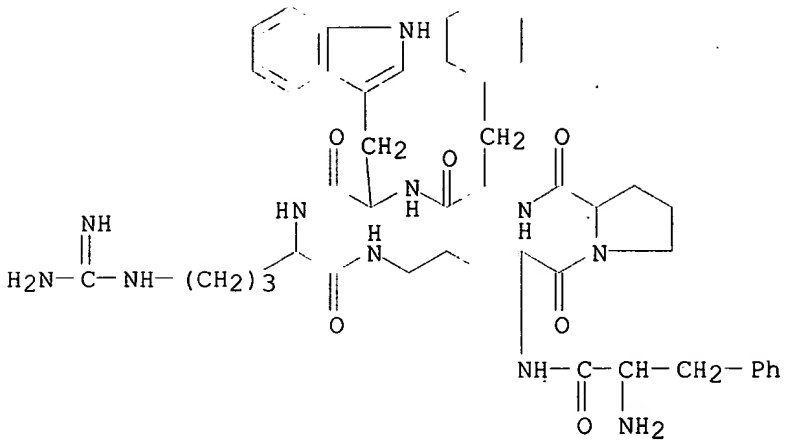
Searched by: Mary Hale 308-4258 CM-1 12D16



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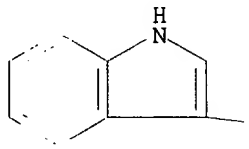
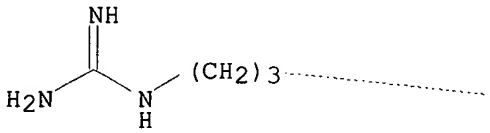
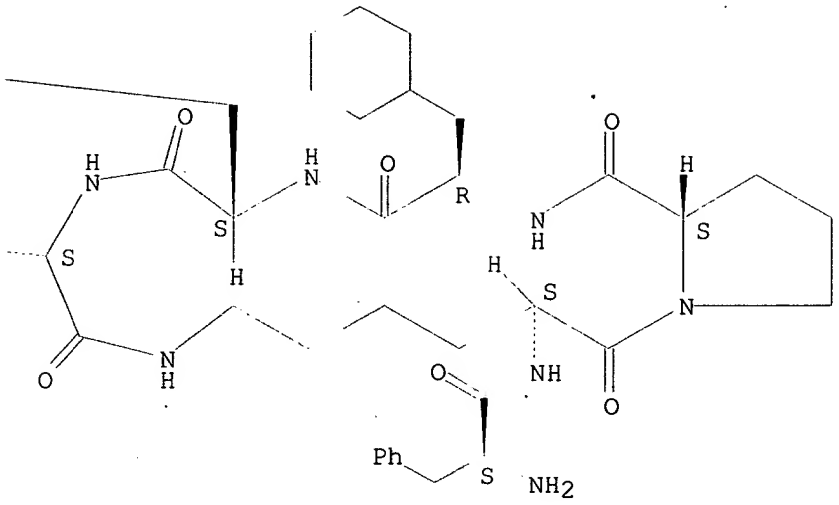
Absolute stereochemistry.

PAGE 1-A





Searched by: Mary Hale 308-4258 CM-1 12D16



L41 ANSWER 7 OF 10 CAPLUS COPYRIGHT 2002 ACS

1999:282834 Document No. 131:96954 Low-Molecular-Weight Peptidic and Cyclic Antagonists of the Receptor for the Complement Factor C5a. Finch, Angela M.; Wong, Allan K.; Paczkowski, Natalii J.; Wadi, S. Khemar; Craik, David J.; Fairlie, David P.; Taylor, Stephen M. (Department of Physiology and Pharmacology and Centre for Drug Design and Development, University of Queensland, Brisbane, 4072, Australia). J. Med. Chem., 42(11), 1965-1974 (English) 1999. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB Activation of the human complement system of plasma proteins during immunol. host defense can result in overprodn. of potent proinflammatory peptides such as the anaphylatoxin C5a. Excessive levels of C5a are assocd. with numerous immunoinflammatory diseases, but there is as yet no clin. available antagonist to regulate the effects of C5a. The authors now describe a series of small mols. derived from the C-terminus of C5a, some of which are the most potent low-mol.-wt. **C5a receptor** antagonists reported to date for the human polymorphonuclear leukocyte (PMN) **C5a receptor**. 1H NMR spectroscopy was used to det. soln. structures for two cyclic antagonists and to indicate that antagonism is related to a turn conformation, which can be stabilized in cyclic mols. that are preorganized for receptor binding. While several cyclic derivs. were of similar antagonistic potency, the most potent antagonist was a hexapeptide-derived macrocycle AcF[OPdChaWR] with an IC50 = 20 nM against a maximal concn. of C5a (100 nM) on intact human PMNs. Such potent C5a antagonists may be useful probes to investigate the role of C5a in host defenses and to develop therapeutic agents for the treatment of many currently intractable inflammatory conditions.

IT **219639-75-5P**

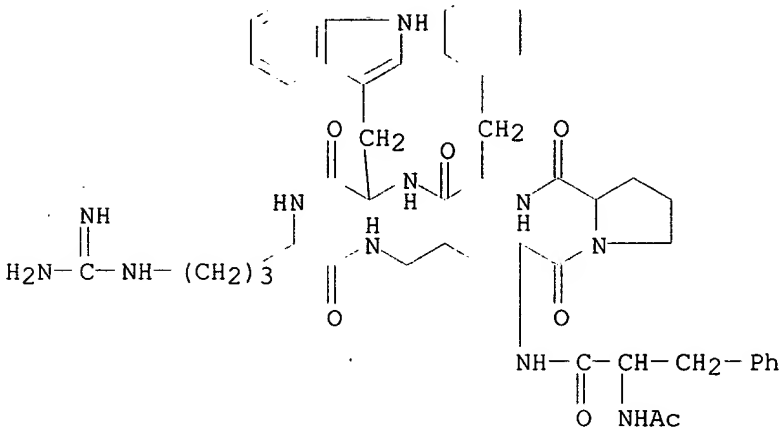
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)

(low-mol.-wt. peptidic and cyclic antagonists of receptor for complement factor C5a on human polymorphonuclear leukocytes in relation to structure and role of complement C5a)

RN 219639-75-5 CAPLUS

Searched by: Mary Hale 308-4258 CM-1 12D16

CN L-Arginine, N-acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



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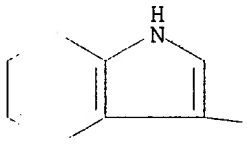
219639-80-2P 219639-81-3P 219639-83-5P
219639-85-7P 219639-88-0P 219639-89-1P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(low-mol.-wt. peptidic and cyclic antagonists of receptor for complement factor C5a on human polymorphonuclear leukocytes in relation to structure and role of complement C5a)

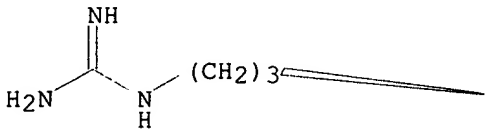
RN 219639-69-7 CAPLUS

CN D-Arginine, N-acetyl-L-phenylalanyl-L-lysyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

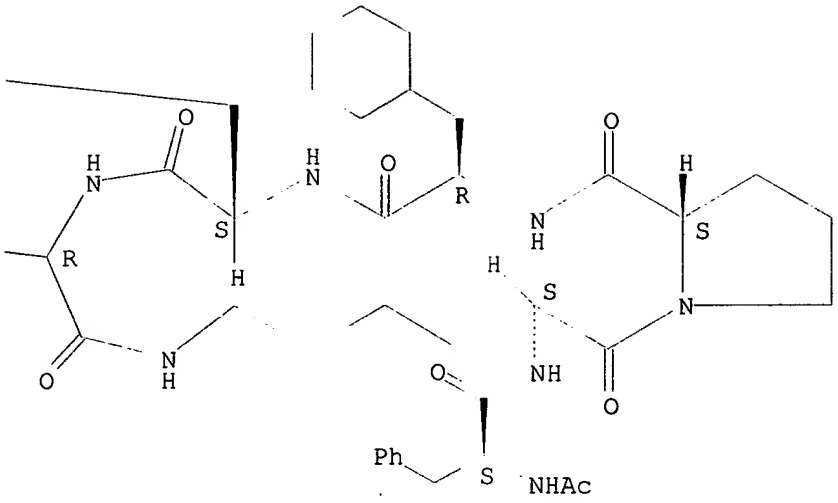
Absolute stereochemistry.

PAGE 1-A





Searched by: Mary Hale 308-4258 CM-1 12D16



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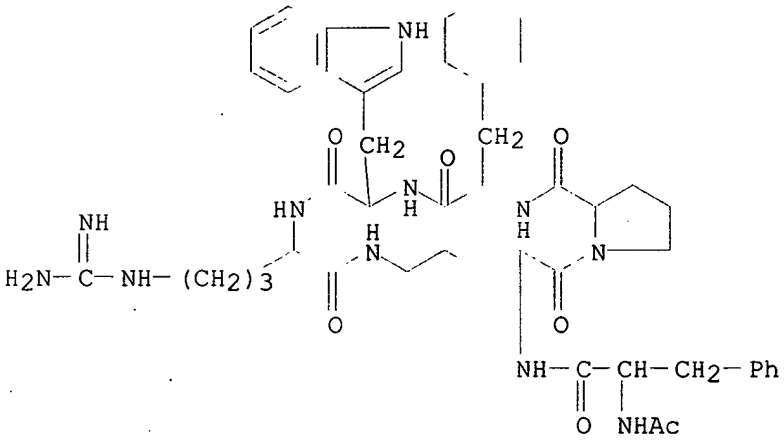

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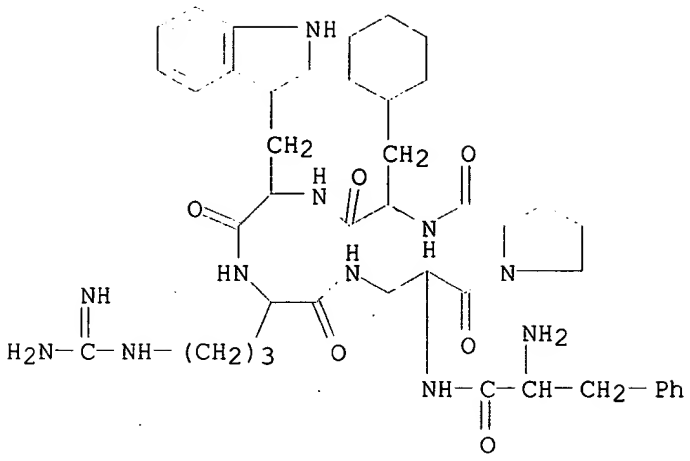
Searched by: Mary Hale 308-4258 CM-1 12D16



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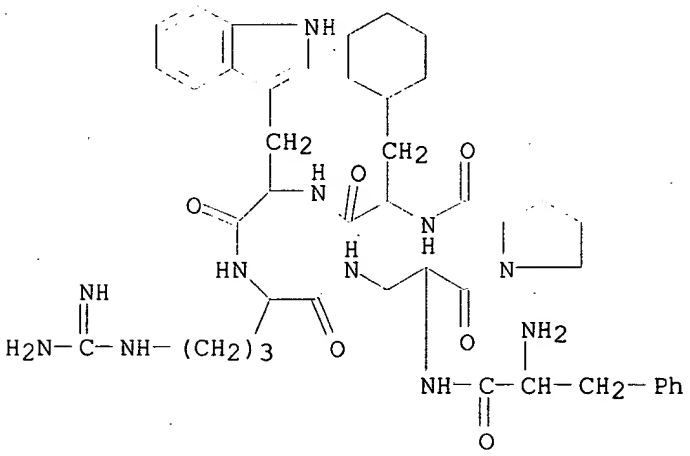

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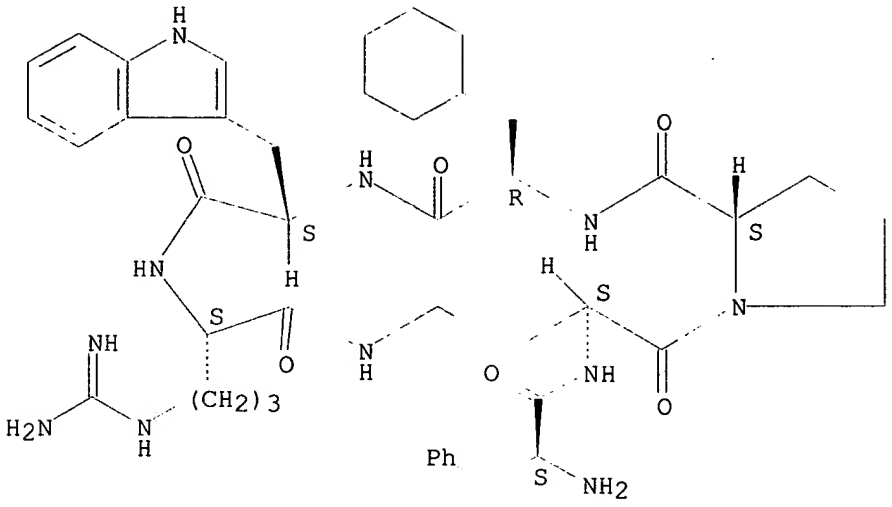
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



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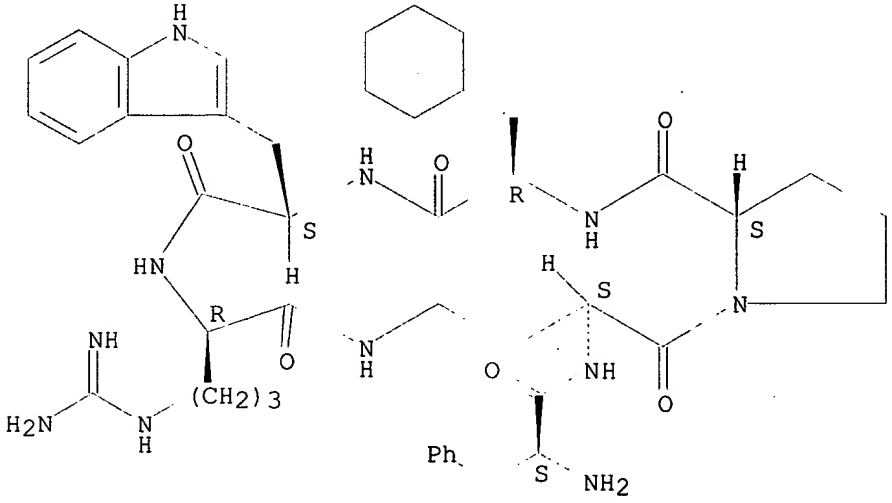
Absolute stereochemistry.



RN 219639-80-2 CAPLUS
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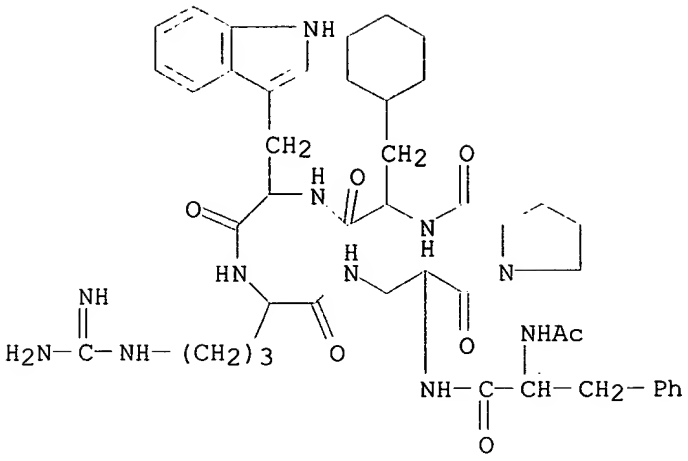
Searched by: Mary Hale 308-4258 CM-1 12D16



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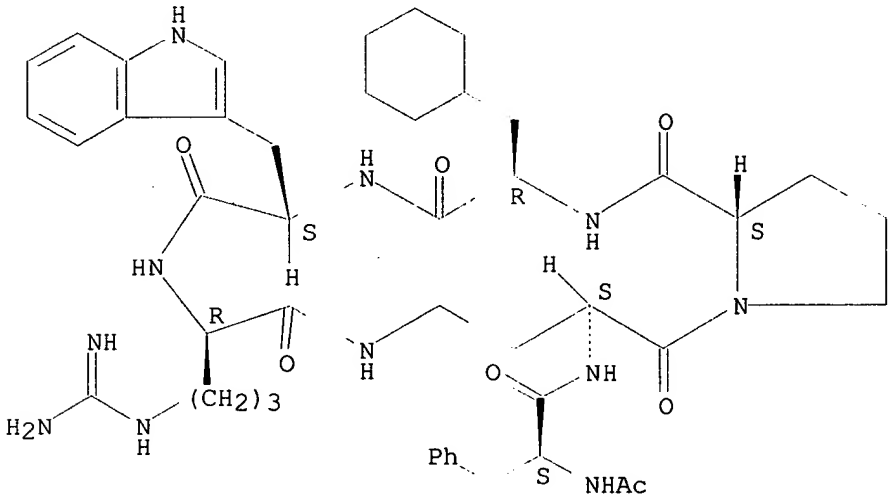
Absolute stereochemistry.



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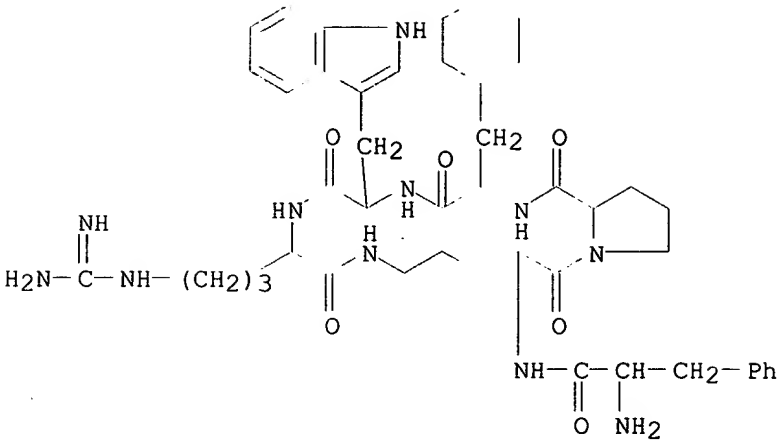
Searched by: Mary Hale 308-4258 CM-1 12D16



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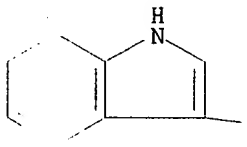
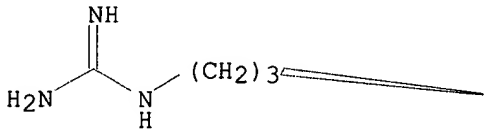
Absolute stereochemistry.

PAGE 1-A





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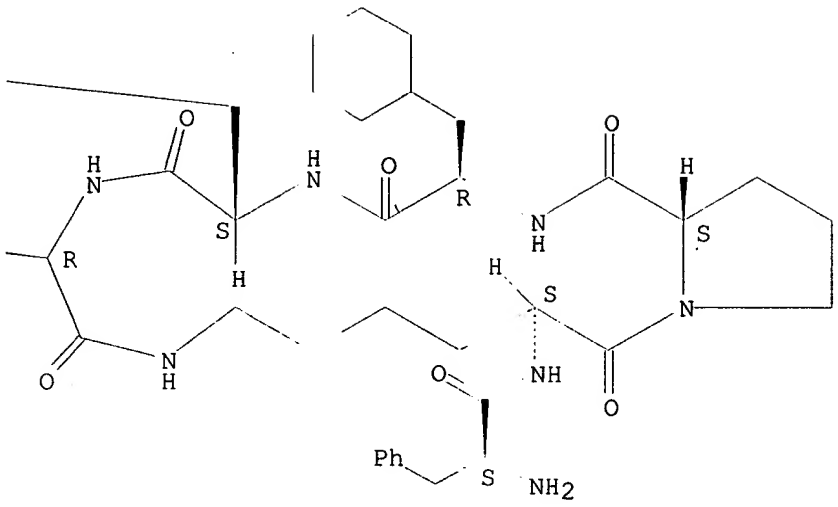

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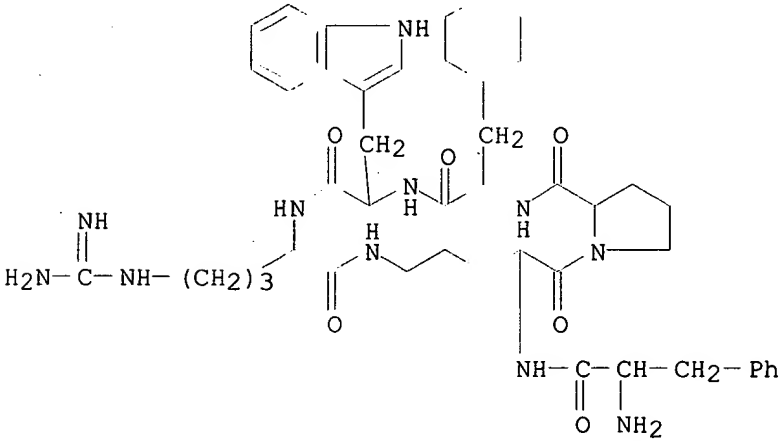

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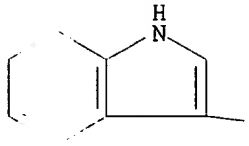
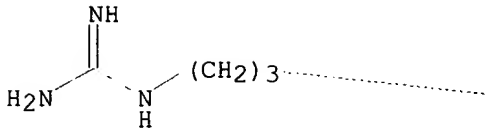
Absolute stereochemistry.

PAGE 1-A





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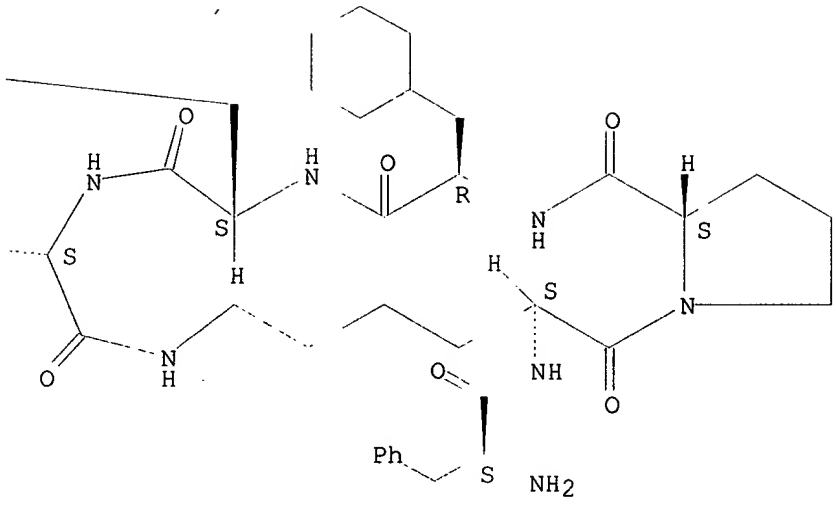

1/12/1

L41 ANSWER 8 OF 10 CAPLUS COPYRIGHT 2002 ACS

1999:810137 Document No. 132:146371 Pharmacological characterization of antagonists of the **C5a receptor**. Paczkowski, Natalii J.; Finch, Angela M.; Whitmore, Jacqueline B.; Short, Anna J.; Wong, Allan K.; Monk, Peter N.; Cain, Stuart A.; Fairlie, David P.; Taylor, Stephen M. (Department of Physiology & Pharmacology, University of Queensland, 4072, Australia). Br. J. Pharmacol., 128(7), 1461-1466 (English) 1999. CODEN: BJPCBM. ISSN: 0007-1188. Publisher: Stockton Press.

AB Potent and highly selective small mol. antagonists have recently been developed by us for **C5a receptors** (C5aR) on human polymorphonuclear leukocytes (PMN). In this study we compared a new cyclic antagonist, F-[OPdChaWR], with an acyclic deriv., MeFKPdChaWr, for their capacities to bind to C5aR on human PMN and human umbilical artery membranes. We also compared their inhibition of myeloperoxidase (MPO) secretion from human PMNs and their inhibition of human umbilical artery contraction induced by human recombinant C5a. In both PMNs and umbilical artery, the cyclic and acyclic C5a antagonists displayed insurmountable antagonism against C5a. There were differences in selectivities for the C5aR with F-[OPdChaWR] (pKb 8.64.+-.0.21) being 30 times more potent than

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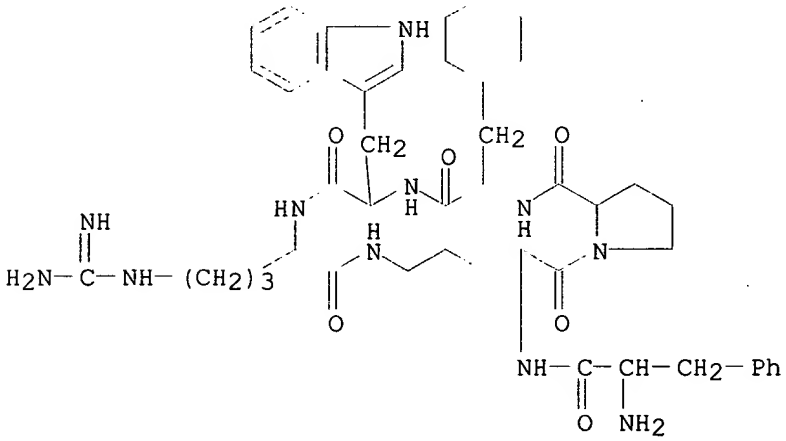
MeFKPdChaWr (pKb 7.16.+-.0.11, P<0.05) in PMNs, but of similar potency (pKb 8.19.+-.0.38 vs pKb 8.28.+-.0.29, resp.) in umbilical artery. This trend was also reflected in their relative binding affinities, both antagonists having similar affinities (-logIC50 values) for C5aR in umbilical artery membranes (F-[OPdChaWR], 7.00.+-.0.46; MeFKPdChaWr, 7.23.+-.0.17), whereas in PMN membranes the C5aR affinity of the cycle F-[OPdChaWR] (7.05.+-.0.06) was four times higher than that of acyclic MeFKPdChaWr (6.43.+-.0.24, P<0.05). In summary, the results reveal that these antagonists are insurmountable in nature against C5a for C5aR on at least two human cell types, and the differences in relative receptor binding affinities and antagonistic potencies against C5a are consistent with differences in receptors within these cell types. The nature of these differences is yet to be elucidated.

IT **219639-88-0**

RL: BSU (Biological study, unclassified); BIOL (Biological study)
(pharmacol. characterization of **C5a receptor** antagonists)

RN 219639-88-0 CAPLUS

CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



L41 ANSWER 9 OF 10 CAPLUS COPYRIGHT 2002 ACS

1999:171134 Document No. 130:347046 Effects of a new **C5a receptor** antagonist on C5a- and endotoxin-induced neutropenia in the rat. Short, Anna; Wong, Allan K.; Finch, Angela M.; Haaima, Gerald; Shiels, Ian A.; Fairlie, David P.; Taylor, Stephen M. (Department of Physiology and Pharmacology, University of Queensland, St. Lucia, 4072, Australia). Br. J. Pharmacol., 126(3), 551-554 (English) 1999. CODEN: BJPCBM. ISSN: 0007-1188. Publisher: Stockton Press.

AB A new **C5a receptor** antagonist, the cyclic peptide Phe-[Orn-Pro-D-cyclohexylalanine-Trp-Arg], (F-[OPdChaWR]), was tested for its ability to antagonize the neutropenic effects of both C5a and endotoxin in rats. Human recombinant C5a (2 .mu.g kg-1 i.v.) caused rapid neutropenia, characterized by an 83% decrease in circulating polymorphonuclear leukocytes (PMNs) at 5 min. Administration of F-[OPdChaWR] (0.3-3 mg kg-1 i.v.), did not affect the levels of circulating PMNs but, when given 10 min prior to C5a, it inhibited the C5a-induced neutropenia by up to 70%. Administration of E. Coli lipopolysaccharide (LPS, 1 mg kg-1 i.v.) also caused neutropenia with an 88% decrease in circulating PMNs after 30 min. When rats were pretreated with F-[OPdChaWR] (0.3-10 mg kg-1 i.v.) 10 min prior to LPS, there was a dose-dependent antagonism of the neutropenia caused by LPS, with up to 69%

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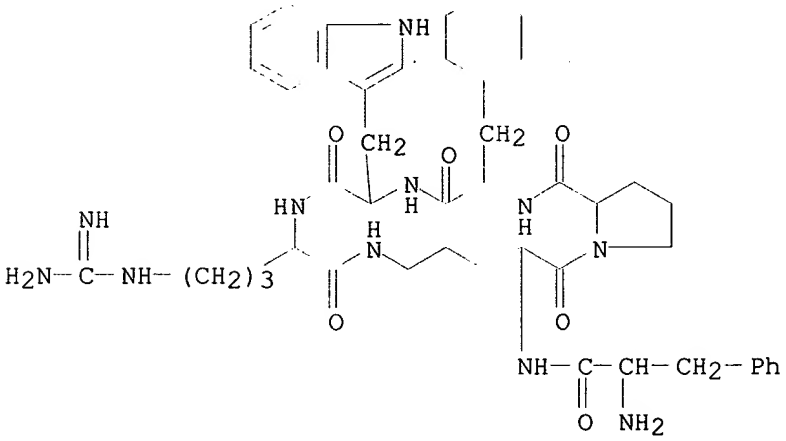
reversal of neutropenia obsd. 30 min after LPS administration. These findings suggest that **C5a receptor** antagonists may have therapeutic potential in the many diseases known to involve either endotoxin or C5a.

IT **219639-88-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**C5a receptor** antagonist effect on C5a- and endotoxin-induced neutropenia)

RN 219639-88-0 CAPLUS

CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



L41 ANSWER 10 OF 10 CAPLUS COPYRIGHT 2002 ACS

1998:503328 Document No. 129:199552 Small molecular probes for **G-protein-coupled C5a receptors**. Conformationally constrained **antagonists** derived from the C terminus of the human plasma protein C5a. Wong, Allan K.; Finch, Angela M.; Pierens, Gregory K.; Craik, David J.; Taylor, Stephen M.; Fairlie, David P. (Centre for Drug Design and Development, University of Queensland, Brisbane, 4072, Australia). J. Med. Chem., 41(18), 3417-3425 (English) 1998. CODEN: JMCMAR. ISSN: 0022-2623. Publisher: American Chemical Society.

AB Activation of the human complement system of blood plasma proteins in response to infection or injury produces a 4-helix bundle glycoprotein (74 amino acids) known as C5a. C5a binds to **G-protein-coupled** receptors on cell surfaces triggering receptor-ligand internalization, signal transduction, and powerful inflammatory responses. Since excessive levels of C5a are assocd. with autoimmune and chronic inflammatory disorders, inhibitors of receptor activation may have therapeutic potential. The authors report soln. structures and receptor-binding and **antagonist** activities for some of the 1st small mol. **antagonists** of C5a derived from its hexapeptide C terminus. The **antagonist** NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO2H (I) surprisingly shows an unusually well-defined soln. structure as detd. by 1H NMR spectroscopy. This is one of the smallest acyclic peptides found to possess a defined soln. conformation, which can be explained by the constraining role of intramol. H bonding. NOE and coupling const. data, slow D2 exchange, and a low dependence on temp. for the chem. shift of the D-Cha-NH strongly indicate an inverse .gamma. turn stabilized by a D-Cha-NH.cntdot..cntdot..cntdot.OC-Lys H bond. Smaller conformational populations are assocd. with a H bond between Trp-

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NH.cntdot..cntdot..cntdot.OC-Lys, defining a type II .beta. turn distorted by the inverse .gamma. turn incorporated within it. An excellent correlation between receptor-affinity and **antagonist** activity is indicated for a limited set of synthetic peptides. Conversion of the C-terminal carboxylate of I to an amide decreases **antagonist** potency 5-fold, but potency is increased .ltoreq.10-fold over I if the amide bond is made between the C-terminal carboxylate and a Lys/Orn side chain to form a cyclic analog. The soln. structure of cycle 6 also shows .gamma. and .beta. turns; however, the latter occurs in a different position, and there are clear conformational changes in 6 vs I that result in enhanced activity. These results indicate that potent C5a **antagonists** can be developed by targeting site 2 alone of the **C5a receptor** and define a novel pharmacophore for developing powerful receptor probes or drug candidates.

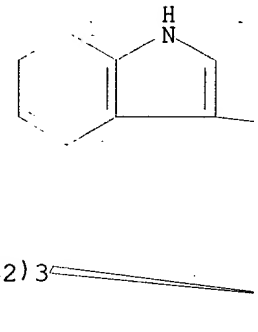
IT **211937-02-9 211937-03-0**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**G-protein-coupled C5a receptors**, conformationally constrained **antagonists** derived from the C terminus of the human plasma protein C5a)

RN 211937-02-9 CAPLUS

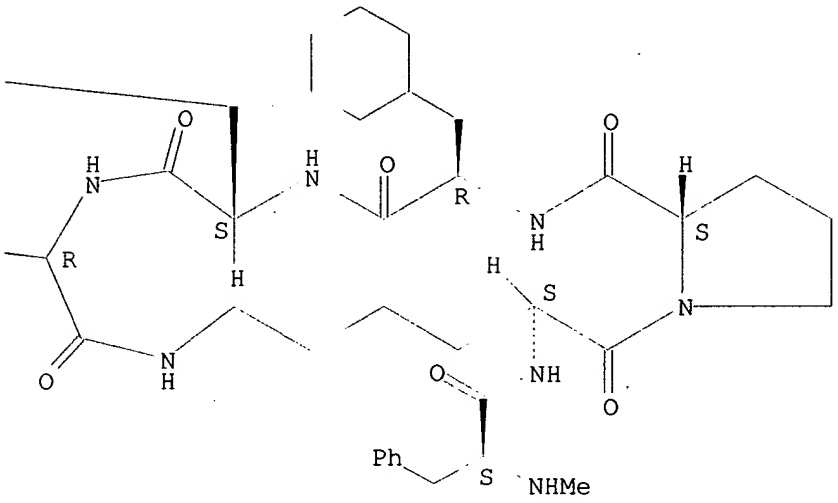
CN D-Arginine, N-methyl-L-phenylalanyl-L-lysyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



Searched by: Mary Hale 308-4258 CM-1 12D16



RN 211937-03-0 CAPLUS
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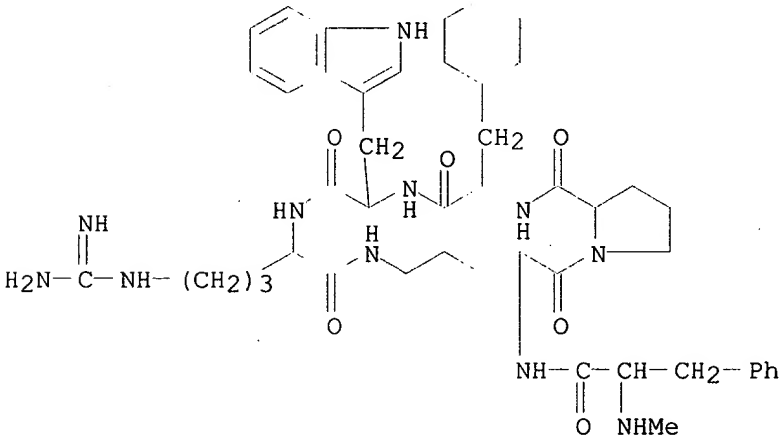

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(FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE, JICST-EPLUS, INSPEC, COMPENDEX, NTIS, WPIDS' ENTERED AT 09:27:59 ON 12 MAR 2002)
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L3            0 S L1 FUL
L4              STR L1
L5           50 S L4
L6              STR L4
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Searched by: Mary Hale 308-4258 CM-1 12D16

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L8         12859 S L6 FUL
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L24            3 FILE CAPLUS
L25            0 FILE BIOSIS
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     TOTAL FOR ALL FILES
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DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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DICTIONARY FILE UPDATES:  10 MAR 2002  HIGHEST RN 400003-05-6

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Calculated physical property data is now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

The P indicator for Preparations was not generated for all of the CAS Registry Numbers that were added to the H/Z/CA/CAplus files between 12/27/01 and 1/23/02. Use of the P indicator in online and SDI searches during this period, either directly appended to a CAS Registry Number or by qualifying an L-number with /P, may have yielded incomplete results. As of 1/23/02, the situation has been resolved. Also, note that searches conducted using the PREP role indicator were not affected.

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L47       31847 FILE BIOSIS
L48       42970 FILE EMBASE

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or systemic lupus erythemat? or tissue graft reject? or ischaemic heart disease or
reperfusion injury or septic shock or psoriasis or gingivitis or atherosclerosis or
alzheimer? disease or multiple sclerosis)
L50          95 FILE MEDLINE
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                 REJECT? OR ISCHAEMIC HEART DISEASE OR REPERFUSION INJURY OR
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=> s l49 and (lung injur? or extracorporeal post dialysis syndrome)
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L57           3 FILE BIOSIS
L58          20 FILE EMBASE

TOTAL FOR ALL FILES
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L62           0 FILE BIOSIS
L63           1 FILE EMBASE

TOTAL FOR ALL FILES
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PROCESSING COMPLETED FOR L64
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L65  ANSWER 1 OF 5  CAPLUS  COPYRIGHT 2002 ACS
2001:935632   Document No. 136:64088  A recombinant cell line expressing
     GPCRx11 as a functional receptor validated by angiopeptin and useful for
     screening of agonists and antagonists.  Lannoy, Vincent; Brezillon,
     Stephane; Detheux, Michel; Parmentier, Marc; Govarts, Cedric (Euroscreen
     S.A., Belg.).  PCT Int. Appl. WO 2001098330 A2 20011227, 46 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,
     HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
     LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG,
     SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ,
     BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY,
     DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE,
     SN, TD, TG, TR.  (English).  CODEN: PIXXD2.  APPLICATION: WO 2001-BE104
     20010620.  PRIORITY: US 2000-PV212913 20000620; US 2000-PV217494 20000711;

Searched by: Mary Hale 308-4258 CM-1 12D16
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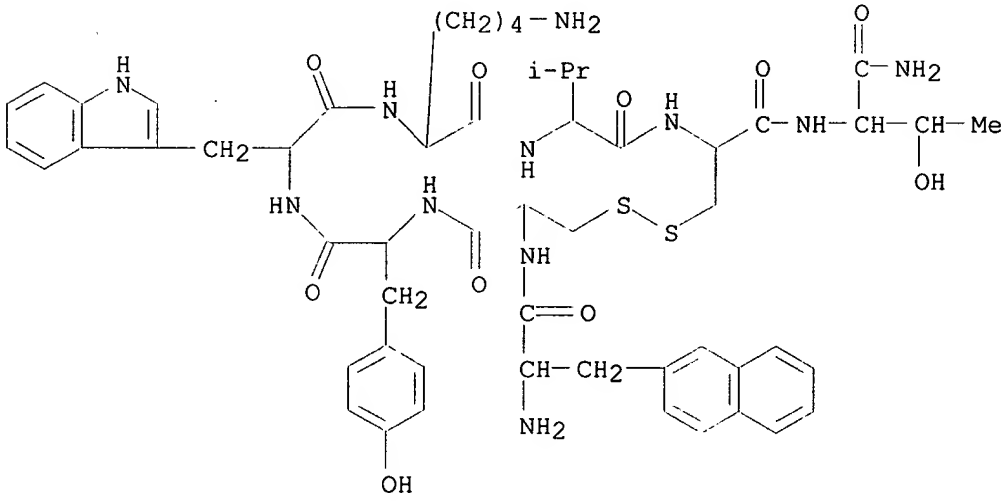
EP 2001-870015 20010126; EP 2001-870024 20010212.

AB The present invention is related to a **G-protein coupled receptor** or GPCRx11 similar to rat RTA receptor (37) and expressed in testis, thymus and uterus. Aequorin cell line expressing GPCRx11 has been used for screening of tissue exts. and ref. ligands. GPCRx11 cells gave a specific signal with synthetic angiopeptin and a somatostatin analog allowing to validate this cell line for screening of natural or synthetic agonists and antagonists. In parallel, extended tissue distribution and polyclonal antibodies have been produced to facilitate GPCRx11 characterization.

IT **108736-35-2 383421-89-4**
RL: PRP (Properties)
(unclaimed sequence; recombinant cell line expressing GPCRx11 as a functional receptor validated by angiopeptin and useful for screening of agonists and antagonists)

RN 108736-35-2 CAPLUS

CN L-Threoninamide, 3-(2-naphthalenyl)-D-alanyl-L-cysteinyl-L-tyrosyl-D-tryptophyl-L-lysyl-L-valyl-L-cysteinyl-, cyclic (2.fwdarw.7)-disulfide (9CI) (CA INDEX NAME)

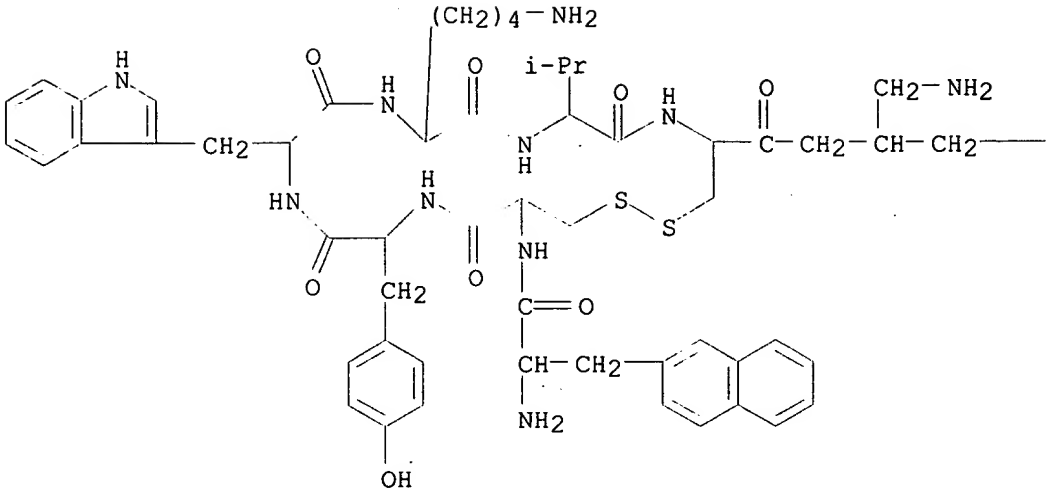


RN 383421-89-4 CAPLUS

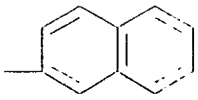
CN 38: PN: WO0198330 PAGE: 15 unclaimed sequence (9CI) (CA INDEX NAME)

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A



PAGE 1-B



L65 ANSWER 2 OF 5 MEDLINE

2001689975 Document Number: 21582002. PubMed ID: 11725163. Synergistic effect of urotensin II with serotonin on vascular smooth muscle cell proliferation. Watanabe T; Pakala R; Katagiri T; Benedict C R. (Department of Internal Medicine, Division of Cardiology, University of Texas-Houston Health Science Center, Houston, Texas 77030, USA.) JOURNAL OF HYPERTENSION, (2001 Dec) 19 (12) 2191-6. Journal code: 8306882. ISSN: 0263-6352. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Urotensin II (U-II), the most potent vasoconstrictor, and serotonin (5-HT) are known to play an important role in pulmonary hypertension. However, little is known about the effect of U-II and its interaction with 5-HT on vascular smooth muscle cell (VSMC) proliferation. OBJECTIVE: We assessed the interaction between U-II and 5-HT in inducing VSMC proliferation. METHODS: Growth-arrested rabbit VSMCs were incubated in serum-free medium with different concentrations of U-II and 5-HT. VSMC proliferation was examined by the increase in [3H]thymidine incorporation into DNA and cell number. RESULTS: U-II or 5-HT induced [3H]thymidine incorporation in a dose-dependent manner with a maximal effect at a concentration of 50 nmol/l (161%) or 50 micromol/l (205%), respectively. When added together, low concentrations of U-II (50 nmol/l) and 5-HT (1 micromol/l) interacted synergistically in inducing [3H]thymidine incorporation (382%). These effects on [3H]thymidine incorporation were paralleled by an increase in cell number. The G-protein inactivator GDP-beta-S (100 micromol/l), protein kinase C (PKC) inhibitor Ro31-8220 (0.1 micromol/l), Src family tyrosine kinase inhibitor PP2 (1 micromol/l), and mitogen-activated protein kinase (MAPK) kinase inhibitor PD098059 (10

micromol/l) inhibited the mitogenic effects of U-II and 5-HT and also their interaction in inducing [3H]thymidine incorporation. CONCLUSION: Our results suggest that U-II and 5-HT may induce the synergistic interaction in inducing VSMC proliferation via a **G-protein-coupled receptor**/PKC/Src tyrosine kinase/MAPK pathway, thus contributing to the relatively rapid development of **atherosclerosis** in hypertensive vascular disease.

L65 ANSWER 3 OF 5 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
2001355537 EMBASE Peptide radiopharmaceuticals for diagnosis and therapy.
Signore A.; Annovazzi A.; Chianelli M.; Corsetti F.; Van de Wiele C.; Watherhouse R.N.; Scopinaro F.. A. Signore, Nuclear Medicine, Policlinico Umberto I, University La Sapienza, 00161 Rome, Italy. alberto.signore@uniromal.it. European Journal of Nuclear Medicine 28/10 (1555-1565) 2001.
Refs: 98.
ISSN: 0340-6997. CODEN: EJNMD. Pub. Country: Germany. Language: English. Summary Language: English.

AB Radiolabelled peptides are an emerging class of radiopharmaceuticals that share chemical and biological properties. From the chemical point of view they have a poly-amino acid structure varying from 3 to more that 200 amino acids, and they are labelled with different isotopes directly or by a linker. Biologically, they bind to specific cell membrane receptors, thus providing in vivo histopathological information for diagnostic purposes, therapy follow-up or targeted radiotherapy. This paper reviews most of the radiolabelled peptides that have been tested in animals and humans in the fields of oncology, neurology, cardiology, inflammation/infection, **atherosclerosis** and thrombosis. A new classification is also proposed for peptides targeting tumour cells based on the biological function of target receptors. These tailored radiopharmaceuticals are the basis of the new era of "molecular nuclear medicine".

L65 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2002 ACS
2000:526444 Document No. 133:276020 Inhibition of C5a-induced neutrophil chemotaxis and macrophage cytokine production in vitro by a new **C5a receptor** antagonist. Haynes, D. R.; Harkin, D. G.; Bignold, L. P.; Hutchens, M. J.; Taylor, S. M.; Fairlie, D. P. (Department of Pathology, University of Adelaide, Adelaide, 5005, Australia). Biochem. Pharmacol., 60(5), 729-733 (English) 2000. CODEN: BCPCA6. ISSN: 0006-2952. Publisher: Elsevier Science Inc..

AB A cyclic peptide, Phe-[Orn-Pro-d-Cyclohexylalanine-Trp-Arg] (F-[OPdChaWR]), was recently shown in vitro to antagonize the binding of C5a to its receptor (CD88) on human polymorphonuclear leukocytes (PMNs) and in vivo to inhibit the neutropenia assocd. with **septic shock** induced by lipopolysaccharide (LPS) in rats. The aim of this study was to investigate whether F-[OPdChaWR] inhibits C5a-mediated chemotaxis of human PMNs using a modified Boyden chamber and C5a-stimulated release of cytokines from human monocytes in vitro. Approx. 50% of the chemotactic activity induced by 10 nM C5a was inhibited by 76 nM F-[OPdChaWR]. This correlated with inhibition of C5a-induced polarization of PMNs by F-[OPdChaWR]. C5a alone failed to induce release of the inflammatory cytokines interleukin(IL)-1.beta., tumor necrosis factor (TNF)-.alpha., and IL-6 from human monocytes at concns. up to 100 nM. However, in the presence of low concns. of LPS (50 ng/mL), both IL-1.beta. and TNF-.alpha. were stimulated by 1 nM C5a. This co-stimulation was inhibited by F-[OPdChaWR] with IC50s of 0.8 and 6.9 nM for release of TNF-.alpha. and IL-1.beta., resp. No agonist activity was detected for F-[OPdChaWR] in either the chemotaxis or cytokine release assays at concns. up to 50 .mu.M. These results show that F-[OPdChaWR] inhibits several important inflammatory activities of C5a and suggest that **C5a receptor** antagonists may be effective in the

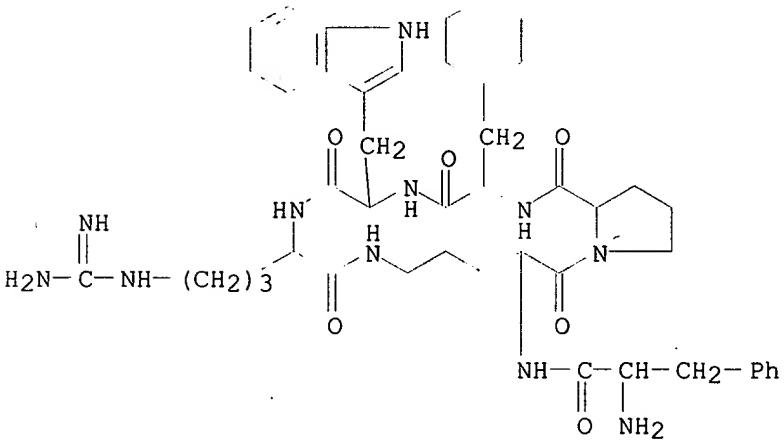
Searched by: Mary Hale 308-4258 CM-1 12D16

treatment of inflammatory diseases mediated by C5a.

IT **219639-88-0**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of C5a-induced neutrophil chemotaxis and macrophage cytokine prodn. in vitro by a new **C5a receptor** antagonist)

RN 219639-88-0 CAPLUS

CN L-Arginine, L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



371

L65 ANSWER 5 OF 5 CAPLUS COPYRIGHT 2002 ACS

1999:34926 Document No. 130:105315 Cyclic agonists and antagonists of **C5a receptors** and **G protein-coupled receptors**. Fairlie, David; Taylor, Stephen Maxwell; Finch, Angela Monique; Wong, Allan (The University of Queensland, Australia). PCT Int. Appl. WO 9900406 A1 19990107, 80 pp. DESIGNATED STATES: W: AU, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-AU490 19980625. PRIORITY: AU 1997-7550 19970625.

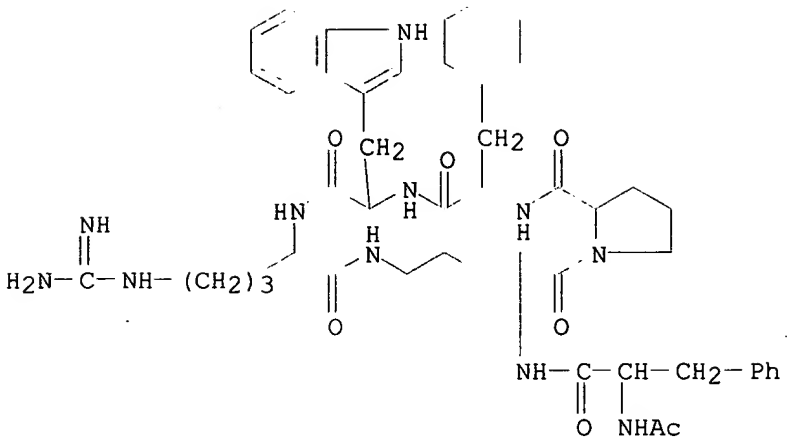
AB Cyclic compds. are provided which have the ability to modulate the activity of **G protein-coupled receptors**. The invention provides both agonists and antagonists. In preferred embodiments, the invention provides cyclic peptidic and cyclic or non-cyclic non-peptidic antagonists or agonists of C5a. The compds. of the invention are both potent and selective, and are useful in the treatment of conditions mediated by **G protein-coupled receptors**, esp. conditions mediated by overexpression or underregulation of C5a, such as a variety of inflammatory conditions.

IT **219639-70-0P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic peptidic and nonpeptidic agonists and antagonists of **C5a receptors** and **G protein-coupled receptors**, and therapeutic use)

RN 219639-70-0 CAPLUS

CN D-Arginine, N-acetyl-L-phenylalanyl-L-ornithyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

Searched by: Mary Hale 308-4258 CM-1 12D16



IT **219639-69-7P**
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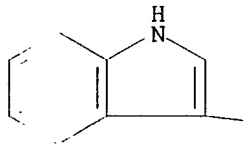
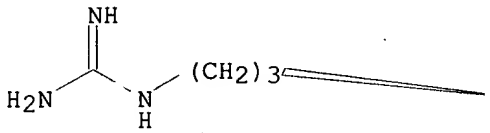
(cyclic peptidic and nonpeptidic agonists and antagonists of **C5a receptors** and **G protein-coupled receptors**, and therapeutic use)
RN 219639-69-7 CAPLUS
CN D-Arginine, N-acetyl-L-phenylalanyl-L-lysyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)

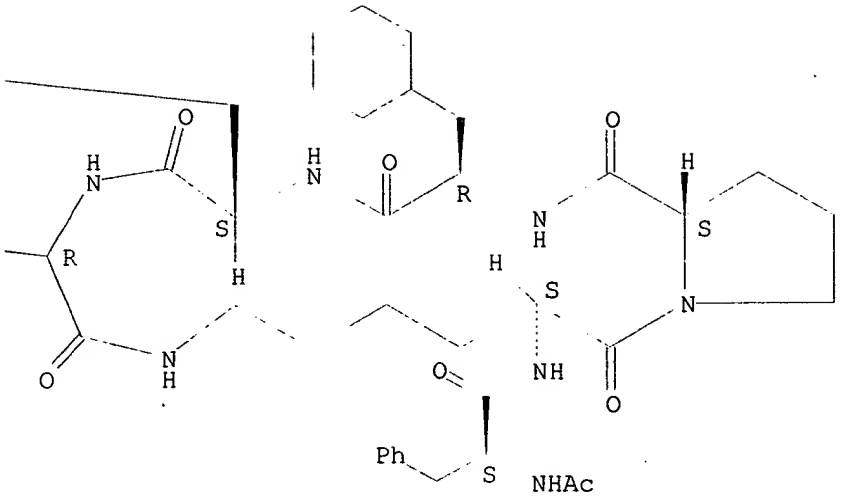
Absolute stereochemistry.

PAGE 1-A





Searched by: Mary Hale 308-4258 CM-1 12D16



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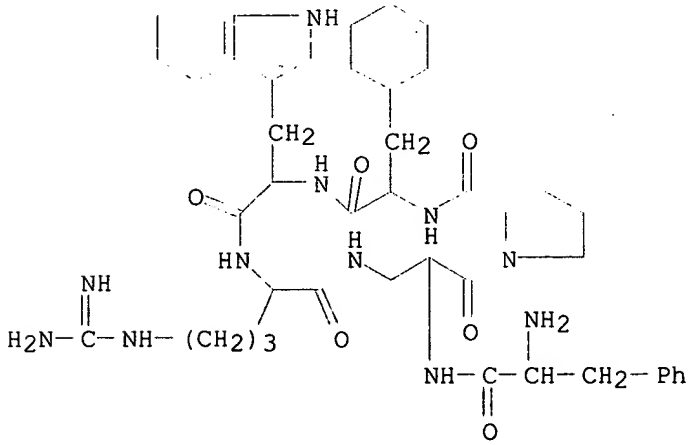
219639-81-3 219639-82-4 219639-83-5
219639-85-7 219639-88-0 219639-89-1
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyclic peptidic and nonpeptidic agonists and antagonists of **C5a receptors** and **G protein-coupled receptors**, and therapeutic use)

RN 219639-71-1 CAPLUS

CN L-Arginine, L-phenylalanyl-3-amino-L-alanyl-L-prolyl-3-cyclohexyl-D-alanyl-L-tryptophyl-, (6.fwdarw.2)-lactam (9CI) (CA INDEX NAME)



RN 219639-72-2 CAPLUS

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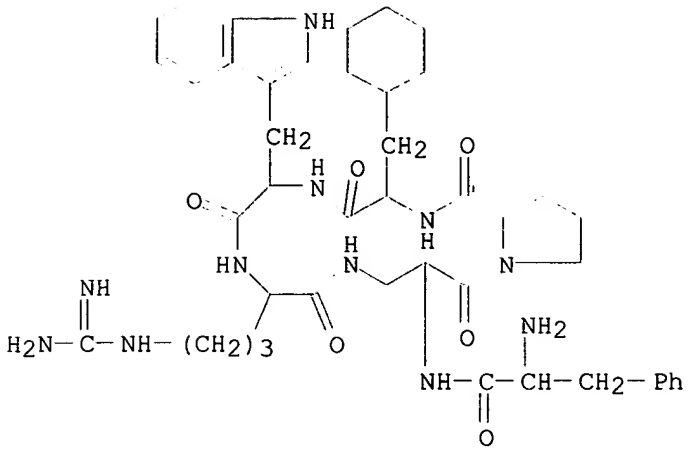
Searched by: Mary Hale 308-4258 CM-1 12D16



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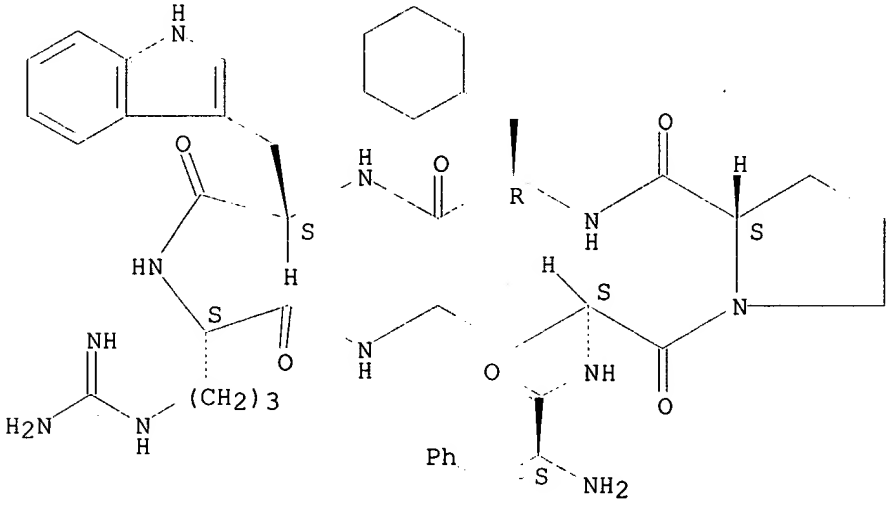
Absolute stereochemistry.



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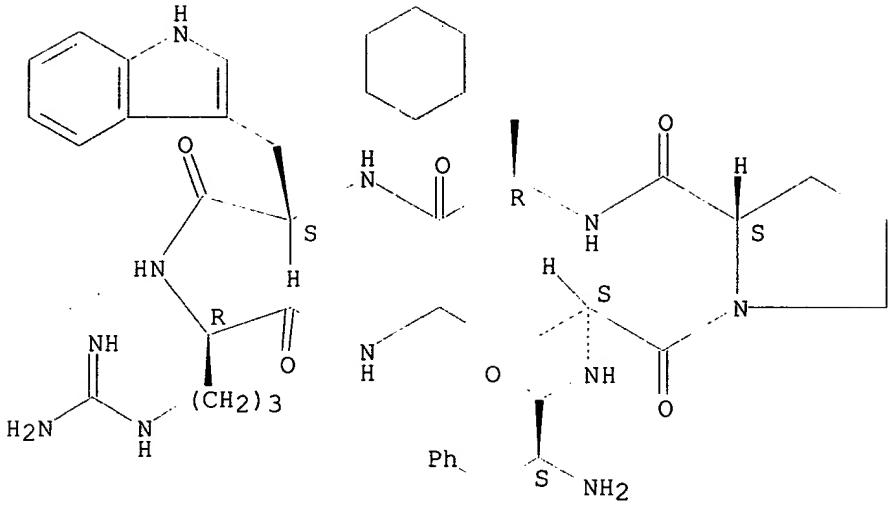
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16



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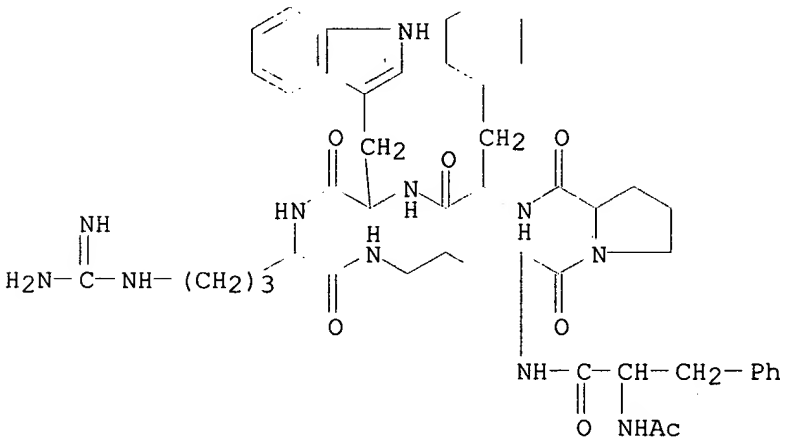

RN 219639-76-6 CAPLUS
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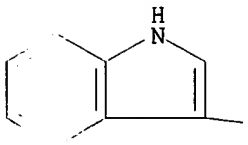
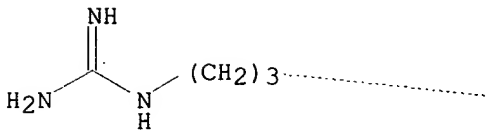
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A





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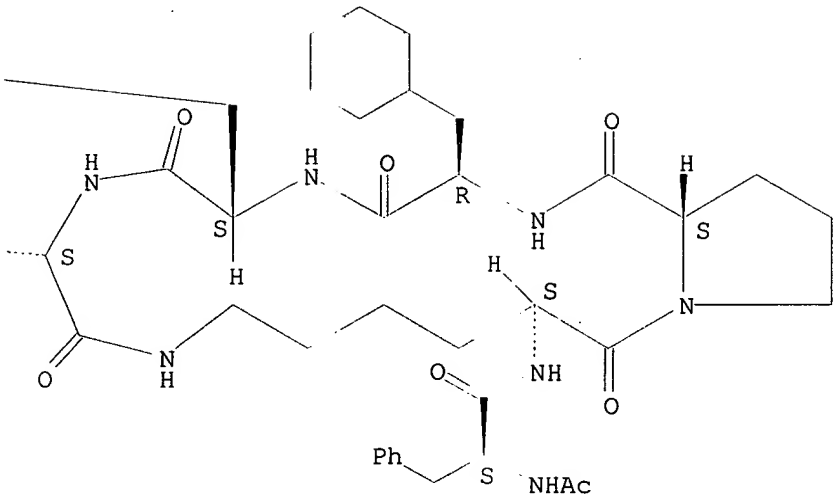

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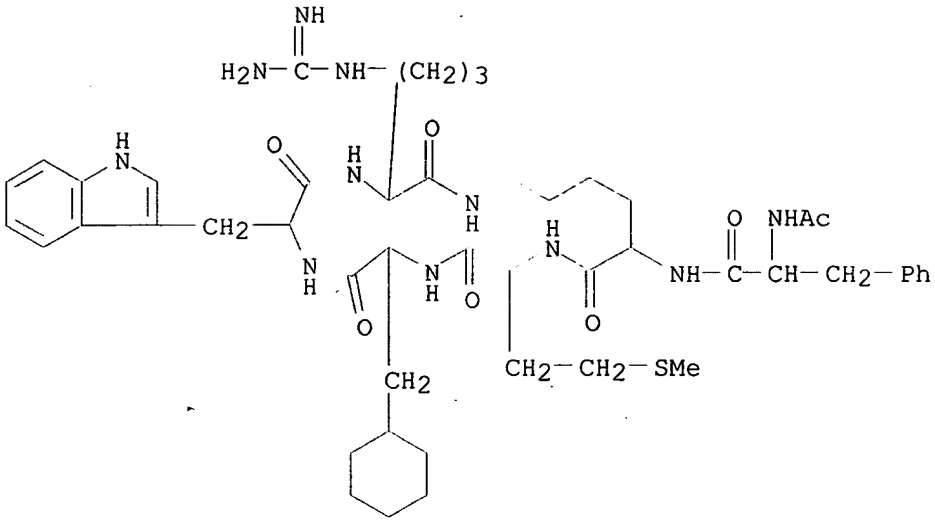
Searched by: Mary Hale 308-4258 CM-1 12D16



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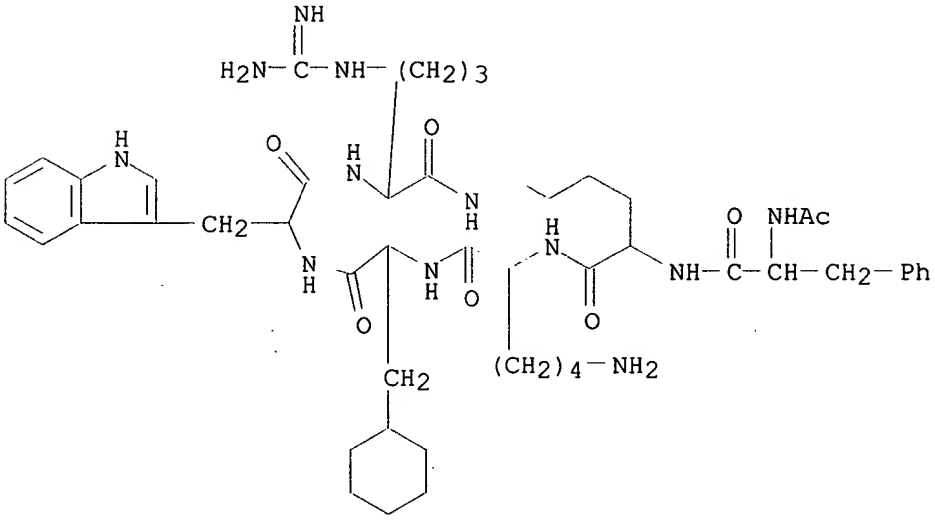

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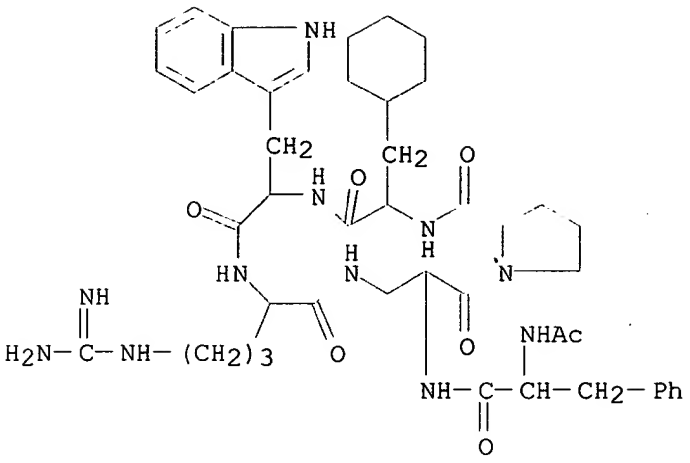
Searched by: Mary Hale 308-4258 CM-1 12D16



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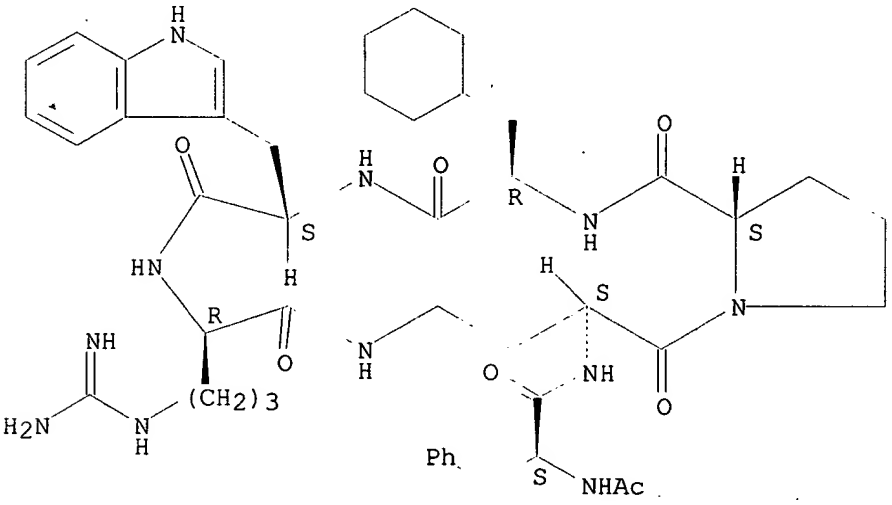
Absolute stereochemistry.



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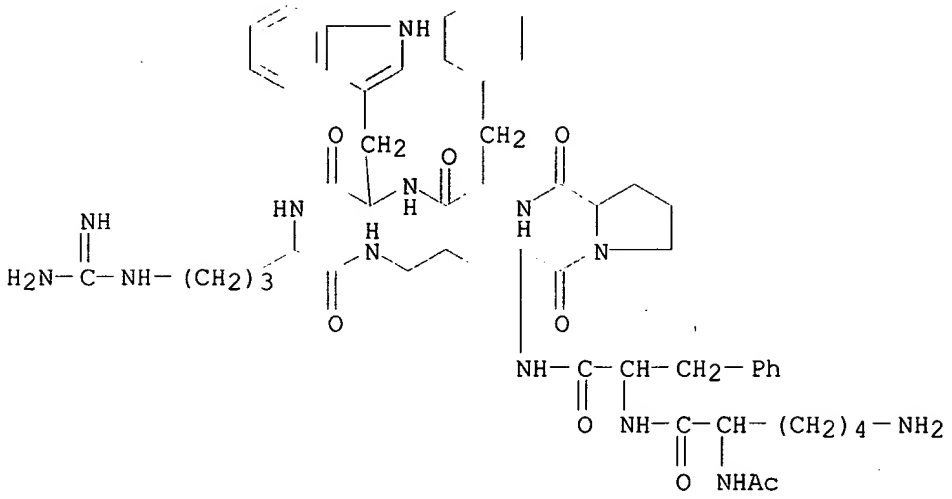
Searched by: Mary Hale 308-4258 CM-1 12D16



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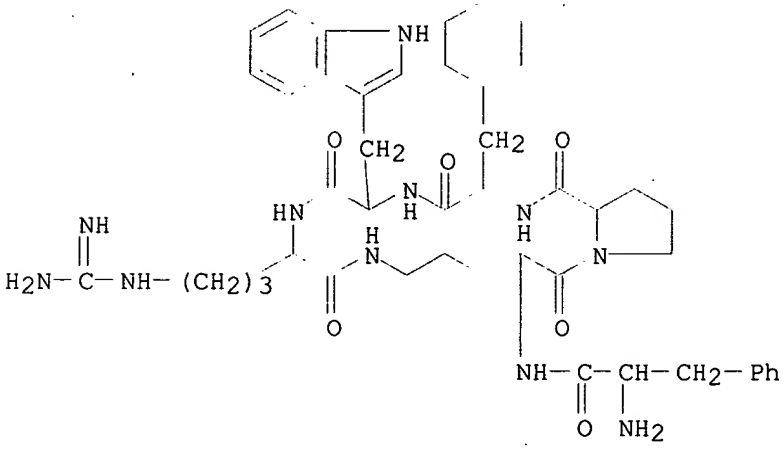

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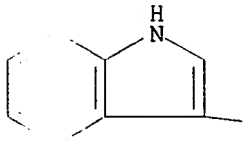
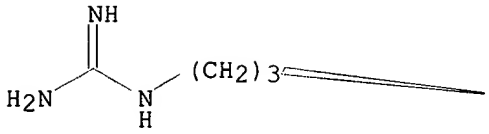
Absolute stereochemistry.

Searched by: Mary Hale 308-4258 CM-1 12D16

PAGE 1-A





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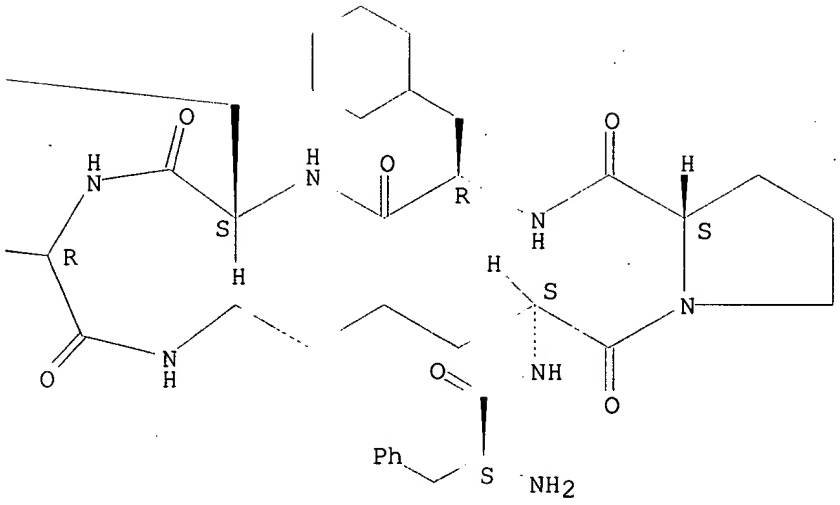

RN 219639-88-0 CAPLUS
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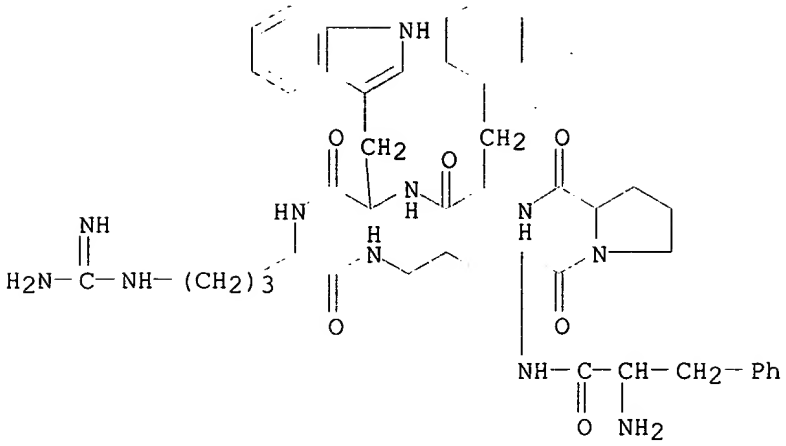
Searched by: Mary Hale 308-4258 CM-1 12D16



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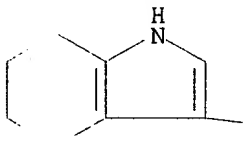
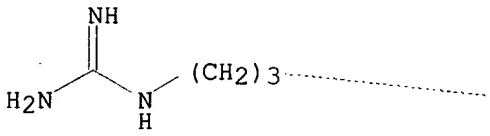
Absolute stereochemistry.

PAGE 1-A





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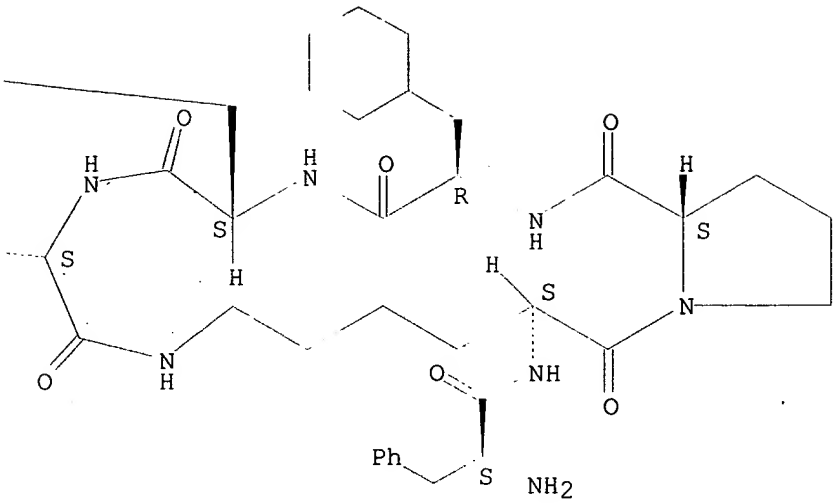

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L68          63 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L69          69 FILE EMBASE

TOTAL FOR ALL FILES
L70         354 FAIRLIE, D?/AU,IN


TAYLOR, IS NOT A RECOGNIZED COMMAND
COMMAND STACK INTERRUPTED.  ENTER "DISPLAY HISTORY"
TO SEE WHICH COMMANDS WERE EXECUTED.

The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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L73        3377 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L74        2058 FILE EMBASE

TOTAL FOR ALL FILES
L75       10610 TAYLOR, S?/AU,IN


'IN' IS NOT A VALID FIELD CODE
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L77         342 FILE CAPLUS
L78         143 FILE BIOSIS
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Searched by: Mary Hale 308-4258 CM-1 12D16

'IN' IS NOT A VALID FIELD CODE
L79 80 FILE EMBASE

TOTAL FOR ALL FILES
L80 733 FINCH, A?/AU,IN

'IN' IS NOT A VALID FIELD CODE
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L82 967 FILE CAPLUS
L83 1157 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L84 752 FILE EMBASE

TOTAL FOR ALL FILES
L85 3638 WONG, A?/AU,IN

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L87 6 FILE CAPLUS
L88 5 FILE BIOSIS
L89 4 FILE EMBASE

TOTAL FOR ALL FILES
L90 19 L70 AND L75 AND L80 AND L85

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L92 1 FILE CAPLUS
L93 5 FILE BIOSIS
L94 4 FILE EMBASE

TOTAL FOR ALL FILES
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PROCESSING COMPLETED FOR L95
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L96 ANSWER 1 OF 6 MEDLINE DUPLICATE 1
1999284666 Document Number: 99284666. PubMed ID: 10354404.
Low-molecular-weight peptidic and cyclic antagonists of the receptor for the complement factor C5a. **Finch A M; Wong A K;** Paczkowski N J; Wadi S K; Craik D J; **Fairlie D P; Taylor S M.** (Department of Physiology and Pharmacology and Centre for Drug Design and Development, University of Queensland, Brisbane, Queensland 4072, Australia.) JOURNAL OF MEDICINAL CHEMISTRY, (1999 Jun 3) 42 (11) 1965-74. Journal code: J0F; 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB Activation of the human complement system of plasma proteins during immunological host defense can result in overproduction of potent proinflammatory peptides such as the anaphylatoxin C5a. Excessive levels of C5a are associated with numerous immunoinflammatory diseases, but there is as yet no clinically available antagonist to regulate the effects of C5a. We now describe a series of small molecules derived from the C-terminus of C5a, some of which are the most potent low-molecular-weight C5a receptor antagonists reported to date for the human polymorphonuclear leukocyte (PMN) C5a receptor. 1H NMR spectroscopy was used to determine solution structures for two cyclic antagonists and to indicate that antagonism is related to a turn conformation, which can be stabilized in

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cyclic molecules that are preorganized for receptor binding. While several cyclic derivatives were of similar antagonistic potency, the most potent antagonist was a hexapeptide-derived macrocycle AcF[OPdChaWR] with an IC50 = 20 nM against a maximal concentration of C5a (100 nM) on intact human PMNs. Such potent C5a antagonists may be useful probes to investigate the role of C5a in host defenses and to develop therapeutic agents for the treatment of many currently intractable inflammatory conditions.

L96 ANSWER 2 OF 6 MEDLINE DUPLICATE 2
2000069032 Document Number: 20069032. PubMed ID: 10602324.
Pharmacological characterization of antagonists of the C5a receptor.
Paczkowski N J; **Finch A M**; Whitmore J B; Short A J; **Wong A K**; Monk P N; Cain S A; **Fairlie D P**; **Taylor S M**.
(Department of Physiology & Pharmacology, University of Queensland, 4072, Australia.) BRITISH JOURNAL OF PHARMACOLOGY, (1999 Dec) 128 (7) 1461-6.
Journal code: B00; 7502536. ISSN: 0007-1188. Pub. country: ENGLAND: United Kingdom. Language: English.

AB 1. Potent and highly selective small molecule antagonists have recently been developed by us for C5a receptors (C5aR) on human polymorphonuclear leukocytes (PMN). In this study we compared a new cyclic antagonist, F-[OPdChaWR], with an acyclic derivative, MeFKPdChaWr, for their capacities to bind to C5aR on human PMN and human umbilical artery membranes. We also compared their inhibition of myeloperoxidase (MPO) secretion from human PMNs and their inhibition of human umbilical artery contraction induced by human recombinant C5a. 2. In both PMNs and umbilical artery, the cyclic and acyclic C5a antagonists displayed insurmountable antagonism against C5a. There were differences in selectivities for the C5aR with F-[OPdChaWR] (pKb 8.64+/-0.21) being 30 times more potent than MeFKPdChaWr (pKb 7.16+/-0.11, $P<0.05$) in PMNs, but of similar potency (pKb 8.19+/-0.38 vs pKb 8.28+/-0.29, respectively) in umbilical artery. This trend was also reflected in their relative binding affinities, both antagonists having similar affinities (-logIC50 values) for C5aR in umbilical artery membranes (F-[OPdChaWR], 7.00+/-0.46; MeFKPdChaWr, 7.23+/-0.17), whereas in PMN membranes the C5aR affinity of the cycle F-[OPdChaWR] (7.05+/-0. 06) was four times higher than that of acyclic MeFKPdChaWr (6.43+/-0. 24, $P<0.05$). 3. In summary, the results reveal that these antagonists are insurmountable in nature against C5a for C5aR on at least two human cell types, and the differences in relative receptor binding affinities and antagonistic potencies against C5a are consistent with differences in receptors within these cell types. The nature of these differences is yet to be elucidated.

L96 ANSWER 3 OF 6 MEDLINE DUPLICATE 3
1999202843 Document Number: 99202843. PubMed ID: 10188960. Effects of a new C5a receptor antagonist on C5a- and endotoxin-induced neutropenia in the rat. Short A; **Wong A K**; **Finch A M**; Haaima G; Shiels I A; **Fairlie D P**; **Taylor S M**. (Department of Physiology and Pharmacology, University of Queensland, St. Lucia, Australia.) BRITISH JOURNAL OF PHARMACOLOGY, (1999 Feb) 126 (3) 551-4.
Journal code: B00; 7502536. ISSN: 0007-1188. Pub. country: ENGLAND: United Kingdom. Language: English.

AB A new C5a receptor antagonist, the cyclic peptide Phe-[Orn-Pro-D-cyclohexylalanine-Trp-Arg], (F-[OPdChaWR]), was tested for its ability to antagonize the neutropenic effects of both C5a and endotoxin in rats. Human recombinant C5a (2 microg kg(-1) i.v.) caused rapid neutropenia, characterized by an 83% decrease in circulating polymorphonuclear leukocytes (PMNs) at 5 min. Administration of F-[OPdChaWR] (0.3-3 mg kg(-1) i.v.), did not affect the levels of circulating PMNs but, when given 10 min prior to C5a, it inhibited the C5a-induced neutropenia by up to 70%. Administration of E. Coli lipopolysaccharide (LPS, 1 mg kg(-1) i.v.) also caused neutropenia with an 88% decrease in circulating PMNs after 30 min. When rats were pretreated with F-[OPdChaWR] (0.3 - 10 mg

kg(-1) i.v.) 10 min prior to LPS, there was a dose-dependent antagonism of the neutropenia caused by LPS, with up to 69% reversal of neutropenia observed 30 min after LPS administration. These findings suggest that C5a receptor antagonists may have therapeutic potential in the many diseases known to involve either endotoxin or C5a.

L96 ANSWER 4 OF 6 MEDLINE DUPLICATE 4
1998387870 Document Number: 98387870. PubMed ID: 9719594. Small molecular probes for G-protein-coupled C5a receptors: conformationally constrained antagonists derived from the C terminus of the human plasma protein C5a. **Wong A K; Finch A M;** Pierens G K; Craik D J; **Taylor S M; Fairlie D P.** (Centre for Drug Design and Development and Department of Physiology and Pharmacology, University of Queensland, Brisbane, Qld 4072, Australia.) JOURNAL OF MEDICINAL CHEMISTRY, (1998 Aug 27) 41 (18) 3417-25. Journal code: JOF; 9716531. ISSN: 0022-2623. Pub. country: United States. Language: English.

AB Activation of the human complement system of plasma proteins in response to infection or injury produces a 4-helix bundle glycoprotein (74 amino acids) known as C5a. C5a binds to G-protein-coupled receptors on cell surfaces triggering receptor-ligand internalization, signal transduction, and powerful inflammatory responses. Since excessive levels of C5a are associated with autoimmune and chronic inflammatory disorders, inhibitors of receptor activation may have therapeutic potential. We now report solution structures and receptor-binding and antagonist activities for some of the first small molecule antagonists of C5a derived from its hexapeptide C terminus. The antagonist NMe-Phe-Lys-Pro-D-Cha-Trp-D-Arg-CO2H (1) surprisingly shows an unusually well-defined solution structure as determined by 1H NMR spectroscopy. This is one of the smallest acyclic peptides found to possess a defined solution conformation, which can be explained by the constraining role of intramolecular hydrogen bonding. NOE and coupling constant data, slow deuterium exchange, and a low dependence on temperature for the chemical shift of the D-Cha-NH strongly indicate an inverse gamma turn stabilized by a D-Cha-NH. OC-Lys hydrogen bond. Smaller conformational populations are associated with a hydrogen bond between Trp-NH.OC-Lys, defining a type II beta turn distorted by the inverse gamma turn incorporated within it. An excellent correlation between receptor-affinity and antagonist activity is indicated for a limited set of synthetic peptides. Conversion of the C-terminal carboxylate of 1 to an amide decreases antagonist potency 5-fold, but potency is increased up to 10-fold over 1 if the amide bond is made between the C-terminal carboxylate and a Lys/Orn side chain to form a cyclic analogue. The solution structure of cycle 6 also shows gamma and beta turns; however, the latter occurs in a different position, and there are clear conformational changes in 6 vs 1 that result in enhanced activity. These results indicate that potent C5a antagonists can be developed by targeting site 2 alone of the C5a receptor and define a novel pharmacophore for developing powerful receptor probes or drug candidates.

L96 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2002 ACS
1997:489769 Conformationally constrained small molecule antagonists of C5a.. **Wong, Allan K.; Finch, Angela M.;** Pierens, Greg K.; **Taylor, Stephen M.; Fairlie, David P.** (Centre Drug Design and Development, University Queensland, Brisbane, 4072, Australia). Book of Abstracts, 214th ACS National Meeting, Las Vegas, NV, September 7-11, MEDI-009. American Chemical Society: Washington, D. C. (English) 1997. CODEN: 64RNAO.

AB Activation of the human complement system of plasma proteins in response to infection or injury produces C5a, a 4-helix bundle glycoprotein of 74 amino acids. C5a binds to G protein-coupled receptors on a range of tissues and cells including mast cells, neutrophils, monocytes, macrophages, etc. Since excessive levels of C5a are assocd. with autoimmune and chronic inflammatory disorders, inhibitors of

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receptor-activation or receptor-internalisation may have therapeutic potential. We now describe the structures and activities of some of the first small mol. antagonists of C5a derived from its hexapeptide C-terminus.

L96 ANSWER 6 OF 6 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
1997:428622 Document No.: PREV199799727825. Conformationally constrained small molecule antagonists of C5a. **Wong, Allan K. (1)**; **Finch, Angela M.**; Pierens, Greg K.; **Taylor, Stephen M.**; **Fairlie, David P. (1)**. (1) Centre Drug Design Dev., Univ. Queensland, Brisbane, QLD 4072 Australia. Abstracts of Papers American Chemical Society, (1997) Vol. 214, No. 1-2, pp. MEDI 9. Meeting Info.: 214th American Chemical Society National Meeting Las Vegas, Nevada, USA September 7-11, 1997 ISSN: 0065-7727. Language: English.

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